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List of Contents

AUTHOR GUIDELINES

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7. Conclusion.
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REFERENCES

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      Nonaka H, Emoto N, Ikeda K, Fukuya H, Rohman MS, Raharjo SB, Yagita K, Okamura H, Yokoyama M. Angiotensin II induces circadian gene expression of clock genes in cultured vascular smooth muscle cells. Circulation. 2001;104:1746-8.
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Editorial

Heart Failure in Indonesia: A Growing Burden Beyond Conventional Care

Vebiona Kartini Prima Putri[1], Siti Elkana Nauli[1], Anggia Chairuddin Lubis[1]

(Indonesian J Cardiol, 2026;47;98-101)

Heart failure (HF) has emerged as one of the most pressing cardiovascular challenges worldwide. Despite major therapeutic advances over the last two decades, HF continues to carry substantial mortality, recurrent hospitalization, impaired quality of life, and economic burden.[1] Globally, more than 64 million people are currently living with HF, and the burden continues to rise alongside population aging, urbanization, and the growing prevalence of cardiometabolic disease.[2] Importantly, the epidemiology of HF in Asia differs significantly from that of Western countries. Patients in Southeast Asia tend to develop HF at a younger age, possess heavier cardiometabolic burdens, and experience worse clinical outcomes despite shorter hospitalization duration.[2-3]

Indonesia reflects this concerning regional pattern. Earlier Indonesian registry data demonstrated that hospitalized HF patients had a mean age of approximately 60 years, substantially younger than many Western HF cohorts, with in-hospital mortality ranging from 6% to 12% and rehospitalization rates approaching 29%.[4] Although national HF registries in Indonesia remain limited in participating centers and patient numbers, available data consistently demonstrate younger HF populations with substantial morbidity and mortality burdens.[4-5] More recent findings from the CORE-HF registry continue to show a high prevalence of hypertension, coronary artery disease, diabetes mellitus, and smoking among Indonesian HF patients, alongside persistent mortality despite implementation of Guideline-Directed Medical Therapy (GDMT).[5]

These observations suggest that Indonesia is no longer facing merely a conventional HF problem, but rather a progressively complex HF epidemic shaped by cardiometabolic disease, recurrent hospitalization, and evolving healthcare system challenges. The growing prevalence of HF with preserved Ejection Fraction (HFpEF), aging populations, chronic kidney disease, obesity, and cardiometabolic syndrome further complicates this landscape, as

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HF management increasingly requires phenotype-based approaches, multimorbidity integration, and multidisciplinary coordination.[1-2]

At the same time, HF management itself has evolved dramatically. Contemporary HF care extends far beyond diuretic therapy and neurohormonal blockade. The modern era of HF encompasses precision phenotyping, multimodality imaging, cardiomyopathy genetics, pulmonary hemodynamics, multidisciplinary transitional care, palliative HF programs, and advanced therapies including cardiac resynchronization therapy, transcatheter interventions, temporary mechanical circulatory support, and Left Ventricular Assist Devices (LVADs).[1] Consequently, advanced HF and transplant cardiology have become recognized competency-based subspecialties in many countries, supported by structured fellowship programs and dedicated multidisciplinary HF systems.[6-7]

Interestingly, Indonesia has already begun entering this era clinically, even if not yet systematically. Dedicated HF clinics are increasingly being established across tertiary centers, cardiomyopathy awareness is improving, and advanced HF discussions are becoming more integrated into routine cardiovascular practice. The emergence of advanced HF services, including the first LVAD implantation in Indonesia, reflects important progress in national cardiovascular care. However, these developments remain concentrated in selected tertiary centers and have yet to translate into an integrated nationwide HF ecosystem.

The major challenge in Indonesia may therefore no longer be whether HF is becoming more advanced, but whether healthcare systems are adequately prepared for it. A growing mismatch appears to exist between the increasing complexity of HF and the readiness of workforce development, healthcare systems, and regulatory support to manage it effectively.

One of the most important barriers lies in workforce development and training. HF care increasingly requires dedicated expertise involving advanced pharmacotherapy, cardiomyopathy evaluation, pulmonary hypertension, device management, mechanical circulatory support, and multidisciplinary coordination. The complexity of modern HF care increasingly exceeds the traditional boundaries of conventional cardiology practice. However, structured, advanced HF training pathways, specialized HF nurses, multidisciplinary HF programs, and integrated transitional HF care remain variably available across institutions, resulting in substantial heterogeneity in HF care delivery. Contemporary HF management increasingly requires competencies that extend beyond conventional cardiology training, including advanced pharmacotherapy, evaluation of cardiomyopathy, pulmonary hemodynamics, and multidisciplinary HF coordination.

Therapeutic inertia further compounds this issue. Although GDMT implementation has improved globally, Southeast Asia continues to demonstrate lower utilization and lower achievement of target-dose HF therapies compared with higher-income regions.[2-3] Delayed optimization of GDMT, concerns regarding tolerability, fragmented follow-up systems, and insufficient multidisciplinary support contribute to persistent gaps between guideline recommendations and real-world practice. In many settings, HF management still focuses predominantly on acute decongestion rather than longitudinal disease modification and vulnerable-phase optimization.

Patient-related barriers also play a substantial role in Indonesia. As the world's largest archipelagic country, Indonesia faces unique geographic disparities in healthcare access. Specialized cardiovascular services remain concentrated in major urban centers, while many patients experience delayed referral, fragmented continuity of care, and limited access to advanced diagnostics or specialist consultation. Additionally, delayed symptom recognition, prolonged exposure to asymptomatic cardiometabolic risk factors, and under-recognition of early HF manifestations may contribute to late presentation and delayed comprehensive evaluation. Low social support, misconceptions regarding polypharmacy, and early symptom improvement after hospitalization may further reduce long-term adherence to HF therapies. In many patients, symptomatic improvement following decongestion may create the perception of recovery, leading to premature discontinuation of long-term disease-modifying therapies. Cultural perceptions toward chronic disease, low health literacy, socioeconomic limitations, and high out-of-pocket healthcare expenditures may further complicate long-term management strategies.[2-3]

Regulatory and healthcare system barriers represent another critical challenge. Although Indonesia has made major progress through the expansion of national universal health coverage, disparities in healthcare resources and access to advanced cardiovascular

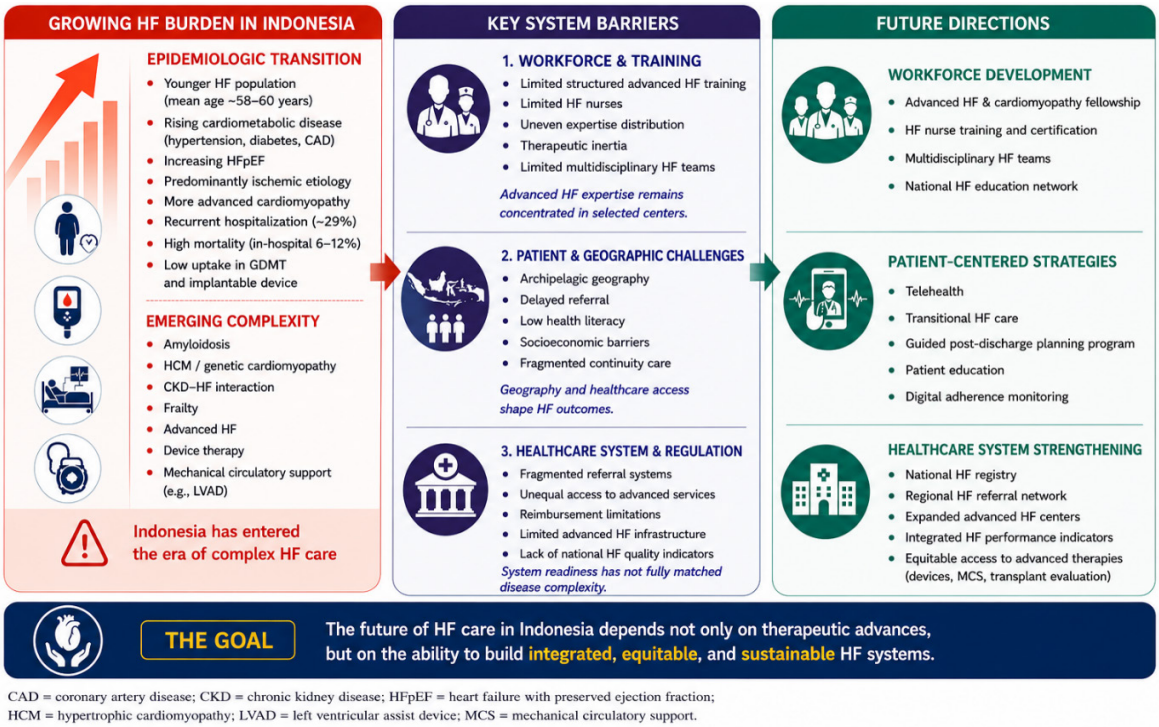

Figure 1. Central Illustration. Toward Integrated and Future-Ready Heart Failure Care in Indonesia.

services remain substantial across regions.[9] Access to advanced HF diagnostics, cardiomyopathy work-up, rehabilitation services, telemonitoring systems, mechanical circulatory support, and structured transitional care remains limited outside selected tertiary centers. Furthermore, HF care pathways are often fragmented, with inconsistent referral systems between primary care, secondary hospitals, and tertiary cardiovascular centers. National HF registries and quality performance indicators also remain underdeveloped, limiting the ability to comprehensively evaluate nationwide HF outcomes.

Importantly, these challenges should not be interpreted as evidence of failure, but rather as signs that Indonesia has entered a new phase of cardiovascular medicine. The epidemiologic transition toward increasingly complex HF inevitably requires evolution in healthcare systems, workforce competency, and policy direction. In many ways, Indonesia is currently experiencing the same transition that previously occurred in developed countries, albeit within different healthcare realities and resource limitations.

Future strategies, therefore, require movement beyond conventional HF care models toward integrated HF systems strengthening. Workforce development should become a major priority, including structured advanced HF and cardiomyopathy training pathways, HF nurse education programs, multidisciplinary HF teams, and broader dissemination of contemporary HF knowledge across healthcare levels. Simultaneously, patient-centered strategies such as telehealth, transitional care programs, digital adherence monitoring, and improved HF education may help bridge geographic and literacy barriers.

Healthcare systems and regulatory frameworks must also continue evolving. Strengthening national HF registries, establishing regional HF referral networks, improving equitable access to advanced therapies, and integrating performance-based HF quality indicators may substantially improve long-term outcomes. Importantly, advanced HF care should not be viewed merely as the provision of sophisticated devices or highly specialized procedures. Rather, advanced HF care fundamentally represents system preparedness: the ability to identify high-risk patients early, optimize evidence-based therapies, coordinate multidisciplinary care, and provide continuity throughout the HF journey.

The burden of HF in Indonesia will continue to rise regardless of healthcare system readiness. As Indonesia's founding President, Soekarno, once encouraged the nation to "dream as high as the sky.

If you fall, you will fall among the stars," the future of HF care in Indonesia may similarly depend on the courage to envision healthcare systems beyond current limitations. Ultimately, the future of HF care in Indonesia will depend not only on therapeutic innovation but also on the ability to build equitable, integrated, and sustainable HF systems capable of serving patients across the continuum of care.

List of Abbreviations

GDMT Guideline-Directed Medical Therapy
HF Heart Failure
HFpEF Heart Failure with Preserved Ejection Fraction
LVAD Left Ventricular Assist Devices

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that Artificial Intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analysis, or conclusions presented in this manuscript

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Editorial

Remembering Eugene Braunwald: Personal Tributes from the Indonesian Cardiovascular Community

Eugene Braunwald Obituary

Teguh Santoso
Medistra Hospital, Jakarta, Indonesia

The world of cardiovascular medicine mourns the passing of Eugene Braunwald, one of the most influential cardiologists of the modern era. Widely regarded as a founding figure in contemporary cardiovascular medicine, he transformed our understanding and treatment of heart disease and shaped the practice of cardiology as we know it today.

Over a distinguished career spanning more than six decades, Dr. Braunwald made pioneering contributions to the pathophysiology and management of coronary artery disease, heart failure, and acute coronary syndromes. His leadership in major clinical trials helped establish evidence-based therapies that remain the cornerstone of cardiovascular care, saving countless lives across the globe.

As the founding editor of Braunwald's Heart Disease, he educated generations of physicians worldwide. More than a textbook, it became a guiding light for clinicians and trainees, reflecting his clarity of thought and relentless pursuit of excellence. Through his mentorship, he shaped not only careers, but the future of cardiology itself.

Born in Vienna in 1929 and forced to flee Nazi-occupied Europe, his journey was marked by resilience and determination. From those early challenges emerged a physician-scientist of extraordinary vision—one who bridged science and clinical care with rare brilliance.

At institutions including Harvard Medical School and its affiliated hospitals, he built environments where discovery, education, and patient care thrived together. Yet beyond his towering academic achievements, he was admired for his humility, discipline, and unwavering dedication to patients.

Even in his later years, Dr. Braunwald remained deeply engaged in advancing the field he helped create—driven by an enduring curiosity and a profound commitment to improving human health.

His passing marks the end of an era. Yet his legacy lives on—in every catheterization laboratory, every heart failure clinic, and every physician inspired by his work. It lives on in the millions of patients whose lives have been extended and improved through the knowledge he helped bring to light.

In remembering Eugene Braunwald, we honor not only a pioneer of cardiology, but a physician who embodied the highest ideals of medicine: intellect, integrity, compassion, and an unwavering devotion to the care of others. He will be deeply missed, and forever remembered.

(Indonesian J Cardiol, 2026;47;102-106)

Eugene Braunwald ObituaryIn Memoriam, Eugene Braunwald, MD, MACC (1929-2026), A Maestro Who Shaped Modern Cardiology

Muhammad Munawar
Chairman, Medical Ethics Committee
Indonesian Heart Association (PERKI)

The Indonesian Heart Association (*Perhimpunan Dokter Spesialis Kardiovaskular Indonesia, PERKI*) joins the global cardiovascular community in mourning the passing of Professor Eugene Braunwald, one of the most influential physician-scientists in the history of modern medicine. His death on 22 April 2026, at the age of 96, marks the end of an extraordinary chapter in cardiovascular science and clinical medicine.[1-2]

For many cardiologists of my generation, especially those who underwent residency training in developing countries such as Indonesia during the 1980s, Professor Braunwald was already a legendary figure long before the era of digital medicine. At that time, there was no internet, no instantly accessible online journals, no YouTube lectures, and certainly no overwhelming flow of medical information through social media. Textbooks were not merely educational materials; they were intellectual companions throughout the demanding years of residency and fellowship training.

Two textbooks stood prominently in the education of cardiology trainees during that period: *Hurst's The Heart and Braunwald's Heart Disease*. While *Hurst* emphasized bedside medicine and clinical reasoning, *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, first published in 1978, provided the rigorous scientific foundation of cardiovascular medicine.[3] Systematic, comprehensive, and academically authoritative, it became the definitive reference for generations of cardiologists worldwide.[3]

Although many of us in Indonesia never had the privilege of meeting Professor Braunwald in person or attending his lectures, we came to know him intimately through his writings, scientific contributions, and intellectual leadership.[1-2] His work shaped the modern understanding of ischaemic heart disease, acute myocardial infarction, heart failure, and cardiovascular therapeutics. His pioneering leadership of the TIMI Study Group transformed the management of acute coronary syndromes and established many of the evidence-based strategies now considered standard of care worldwide.[2]

Professor Braunwald's scientific achievements were immense. He was among the first investigators to demonstrate the progressive nature of myocardial necrosis and the importance of early reperfusion, laying the conceptual foundation for the principle that "time is muscle."[4] He also contributed fundamentally to the clinicopathologic and therapeutic foundations of modern cardiology, including the study of valvular heart disease, coronary syndromes, and post-infarction ventricular remodeling.[1-6]

In collaboration with John Ross Jr and colleagues, he contributed to landmark studies of aortic stenosis, ventricular function, and the concepts of afterload mismatch and preload reserve.[1,5] Their observations demonstrated that the onset of symptoms in severe aortic stenosis—angina, syncope, and heart failure—is associated with a steep decline in survival, thereby defining the need for timely valve intervention.[5]

Braunwald's influence extended beyond pathophysiology to therapeutics and long-term outcomes. Experimental work on infarct size after coronary occlusion helped establish the biologic rationale for early reperfusion therapy in acute myocardial infarction.[4] Later, clinical studies, such as the SAVE trial, clarified the role of angiotensin-converting enzyme inhibition in preventing adverse left ventricular remodeling after myocardial infarction and in reducing cardiovascular mortality.[6] Together, these advances helped cement the evidence-based approach that characterized his era.[1-2]

Yet beyond his scientific accomplishments, Professor Braunwald represented something even greater for physicians in countries far from the world's major academic centers. He symbolized intellectual discipline, scientific curiosity, humility, and lifelong dedication to medicine. Through his textbooks and publications, he taught generations of young cardiologists not only to understand cardiovascular disease but also to think critically and to care deeply for patients.[1-3]

On a personal level, his impact on my professional journey has been profound, even though I never met him. I vividly remember a meaningful moment after completing my fellowship training in electrophysiology at Austin Hospital, Melbourne, when my mentor, Professor Andrew Tonkin FRACP, kindly asked what gift I would like to receive as a remembrance from the institution. Without hesitation, I requested a copy of *Braunwald's Heart Disease*. To me, the book represented far more than a textbook; it symbolized a lifelong journey in cardiology and a connection to the intellectual legacy of Professor Eugene Braunwald himself.[3]

The passing of Professor Braunwald is therefore deeply felt, including by the cardiology community in Indonesia. Even from afar, his influence reached our hospitals, classrooms, coronary care units, catheterization laboratories, and training programs. Countless Indonesian cardiologists have learned from his writings, referenced his studies on aortic stenosis, infarct size limitation, and ventricular remodeling, and practiced medicine guided by principles that he helped to establish.[3,5-6]

His legacy transcends institutions, countries, and generations. It lives on in the millions of patients whose lives have been improved or saved through advances in cardiovascular medicine that he helped pioneer.[1-2,4,6] It continues through the physicians, researchers, educators, and trainees inspired by his example. On behalf of PERKI and the Indonesian cardiovascular community, we express our deepest gratitude and respect for Professor Eugene Braunwald. Farewell, Professor Braunwald. May you rest in eternal peace.

Father of Modern Cardiology

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While Eugene Braunwald was widely known as the "Father of Modern Cardiology," my first "contact" with him was through his textbook, Braunwald's Heart Disease, when I was a cardiology resident. The textbook was our main resource during our cardiology residency to build a broad understanding of the field. Many of us do not know him personally, but knowing his academic works, including his books, research, scientific talks, and other scientific works, we understand that he was a visionary and brilliant person, a great educator, and a leading cardiologist of his time with a global influence. His dedication to the academic world was extraordinary. He had never stopped inspiring us to be the best versions of ourselves, using his long life to produce something valuable for the next generation, and he had always remained relevant to any period of which he lived. Braunwald's legacy is not just about his academic works but also about the way he lived his life, with hard work, dedication, and integrity. He was an excellent role model whom we can emulate and whose principles we can apply to our professional lives, continuing his legacy for a brighter future in cardiology.

Echoes of Inspiration: Remembering Eugene S. Braunwald

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I feel, in many ways, unworthy to offer a few words about the father of modern cardiology. I never had the privilege of meeting or conversing with him. What kind of personal testimony can I truly provide? I know him as a legend. And that is precisely how I will remember and describe him in these passages.

I consider myself a young cardiologist (hopefully still true in the eyes of my colleagues). It was 17 years ago, during my cardiology clinical rotation in medical school, that both my seniors and attending consultants emphasized one essential

resource for surviving this demanding period: *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*.[3] It was regarded as mandatory reading material for any medical students rotating through cardiology. It was still an age when we needed to look up the glossary or the table of contents to find where a specific disease was being discussed. Yet even then, I clearly remember noticing the name Eugene S. Braunwald inscribed on the back cover.

I can only begin to imagine the magnitude of his legacy and its impact on generations of physicians. How many patients have been successfully treated because their doctors learned from that book? How many research questions were inspired by ideas explored within its chapters? How many physicians found their calling in cardiology after reading its preface and foreword? (I was one of them). It remains a personal regret that I never had the opportunity to be in the same room with him. Otherwise, I would have eagerly sought to engage in a conversation. And perhaps a photograph to commemorate meeting someone who profoundly influenced my path.

I have read numerous testimonials from renowned figures in cardiology who knew him personally.[1,7] Their accounts affirm that his legacy is no exaggeration. He is consistently described as resilient, hardworking, deeply committed, unwavering in his dedication, and humble. Qualities that I hope each of us can one day achieve.

We will always be there to ensure his name continues to echo across generations of cardiologists. A founding figure of modern cardiology who witnessed (and actively shaped) multiple eras of diagnostic and therapeutic advancement over more than 6 decades.[7] He not only observed the evolution of cardiology but remained a central contributor throughout it. His passion and dedication are undeniably contagious. Those who know of him carry forward his legacy, striving to contribute meaningfully to the field he helped define.

Exhibit A: The Mechanical Maestro and the Left Main Coronary

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Cardiologist at RSUD Berkah Pandeglang, Pandeglang, Indonesia
Developer of CardiologyVault

I have never shaken the hand of Eugene S. Braunwald, nor have I ever stood within the same geographical zip code as his legendary fountain pen. To me, he exists entirely as a highly organized rumor. A towering, mythical figure rendered in 11-point font across several thousand pages of heavy, cream-colored paper.

My obsession with his architecture began during the sleepless, clueless, and distinctly unskilled nights of my medical school clinical rotation. At the time, I was a young, perpetually exhausted student carrying a stethoscopic kit that was far too large for my pockets. The senior physicians, a group of stern individuals with perfectly combed hair, pointed toward a massive, cloth-bound brick of a volume. It was an object designed for heavy lifting, frequently used as a counterweight to hold down unstable stacks of patient charts.

It was *Braunwald's Heart Disease*. Navigating its dense interior required a transparent ruler and a steady thumb on the glossary. Yet, upon reading his preface, a strange, precise gear clicked inside my mind. I realized I did not merely want to practice medicine; I wanted to decode the absolute geometry of the human circulatory system. I became fascinated by the sheer, unadulterated knowledge behind hemodynamics, the strict, beautiful laws of pure physics neatly wrapped in the nomenclature of Cardiology. I decided right then to become a cardiologist.

If one were to sketch a cross-section of modern cardiovascular science, Dr. Braunwald's initials would be found stamped upon every single valve, catheter, and randomized clinical trial of the last sixty years. He did not merely watch the historical transition from rudimentary wooden stethoscopes to complex, high-resolution fluoroscopy; he actively curated the timeline. He treated the coronary tree not as a chaotic bundle of organic tissue, but as a magnificent, temperamental Swiss timepiece that required absolute, microscopic precision to repair.

The Chief Architect has officially left the building. He has packed his slide rules, adjusted his spectacles, and turned off the green-shaded lamp in his study. But for those of us who spend our days navigating the narrow, delicate channels of the human heart, we will continue to keep his machinery running, immaculately oiled, perfectly calibrated, and precisely on time.

Furthermore, I make this distinct, solemn promise: the name of the Indonesian Cardiologist will eventually echo across the global theater. We will contribute to this mechanism, perhaps not with a roar as loud as his, but with a voice entirely distinct, perfectly measured, and large enough to be recognized widely on the world stage.

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Original Article

The Association Between LDL Levels and Heart Failure Incidence in Patients with Acute Myocardial Infarction: Observational Study

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Abstract

Background: Acute Myocardial Infarction (AMI) is one of the leading causes of cardiovascular morbidity and mortality worldwide. A serious complication that can arise from AMI is heart failure, which can significantly worsen the patient's prognosis. Low Density Lipoprotein (LDL) is recognized as a major risk factor for atherosclerosis and plays a critical role in the pathophysiology of AMI. This study aims to determine whether there is an association between LDL levels and the incidence of heart failure in patients with acute myocardial infarction.

Methods: This observational study used medical records from Purwokerto Islamic Hospital (January 2022-December 2024) relating to patients diagnosed with acute myocardial infarction, regardless of the presence of heart failure. LDL levels were categorized as optimal or non-optimal using a cut-off level of 100 mg/dL. Bivariate analysis was performed using RStudio, while baseline characteristics that were classified by the presence or absence of heart failure status were examined with SPSS software platform.

Results: Statistical analysis using the Chi-square test revealed a significant association between LDL levels and the incidence of heart failure in patients with acute myocardial infarction at Islamic Hospital Purwokerto, with a p-value of 3.52e-10/ < 0.05.

Conclusions: Higher LDL levels are significantly associated with an increased risk of heart failure in AMI patients, highlighting the importance of LDL control. Further studies should consider additional factors like infarct size, myocardial injury, hypertension, diabetes, ejection fraction, and the role of inflammation for a more comprehensive risk assessment.

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Introduction

Acute Myocardial Infarction (AMI) constitutes a critical and potentially fatal coronary incident linked with Sudden Cardiac Death (SCD), representing the most extreme clinical expression of coronary artery disease. This condition can be classified into two subtypes: ST-Elevation Myocardial Infarction (STEMI) and non-ST-Elevation Myocardial Infarction (NSTEMI). Given that unstable angina often precedes the onset of AMI, it is also recognized as a form of Acute Coronary Syndrome (ACS).[1]

Myocardial Infarction (MI) is a major contributor to cardiovascular diseases, which are the world's leading cause of death. In 2016, they caused 17.9 million deaths, making up 31% of global deaths. Over 75% of these deaths occurred in developing countries, with low- and middle-income nations accounting for 82% of all cardiovascular disease deaths.[2]

AMI frequently results in heart failure, an undesirable side effect. Depending on patient characteristics, treatment techniques, and follow-up period, the cumulative incidence of Heart Failure (HF) following AMI in contemporary cohorts can range from 10% to over 30%. According to Jenča et al.'s comprehensive meta-analysis and review, for example, the development of HF following MI significantly lowers the prognosis and continues to be a major worldwide health burden.[3]

Low-Density Lipoprotein Cholesterol (LDL-C) is a crucial factor in the context of lipid metabolism in atherosclerosis, activating endothelial cells to produce pro-inflammatory molecules, impairing vasodilation, increasing monocyte infiltration, promoting foam cell formation, and stimulating smooth muscle cell proliferation. One obvious risk factor for cardiovascular disease is elevated LDL-C levels, with a direct correlation between LDL-C levels and the inflammatory burden in individuals who have suffered an AMI.[4-5] the division of LDL levels can be categorized into optimal and non-optimal, with a threshold value of 100 mg/dL.[6]

AMI leads to HF through myocardial damage, ischemia, mechanical complications (e.g., papillary muscle rupture), cardiomyocyte changes, progressive necrosis, reperfusion-induced damage via Reactive Oxygen Species (ROS), thrombotic embolization causing microvascular dysfunction, and inflammation from myocyte death.[3] Despite established links between Low-Density Lipoprotein (LDL) levels and cardiovascular diseases, the specific association among patients with AMI, elevated LDL levels, and the incidence of HF remains underexplored, leaving a critical gap in understanding how lipid profiles, particularly LDL, influence HF development. This study aims to fill this gap, potentially guiding more targeted interventions to prevent HF in high-risk patients, ultimately improving patient outcomes and reducing healthcare burdens.

Methods

A cross-sectional, observational, analytic, quantitative design was used in this study to determine the relationship between LDL levels and the incidence of HF among patients with AMI at Purwokerto Islamic Hospital. The location of this study was Purwokerto Islamic Hospital in Banyumas Regency, Central Java. This study was conducted in January-February 2025 using patients' electronic medical records. This research has received ethical approval from the Purwokerto Islamic Hospital.

The study population consisted of inpatients diagnosed with AMI. Consecutive sampling was used to select participants based on defined inclusion and exclusion criteria. The sample size was determined using GPower 3.1.9.7 software (Heinrich Heine University Düsseldorf, Germany)[7], with an effect size of 0.3 (medium), a significance level of $p < 0.05$, and a statistical power of 84%. Based on these parameters, the final sample size was 97.

Inclusion criteria for this study are patients diagnosed with AMI, identified from retrospective data collected from January 2022 to December 2024. There is data on the results of the first LDL level examination in the patient's electronic medical record, and there are complications in the form of HF. In this study, we confirmed the complications of HF based on data written in the electronic medical record by the doctor in charge of the patient, wrote the degree of HF based on Killip criteria, attached chest x-ray images, and administered furosemide therapy. Exclusion criteria included patients who were diagnosed with HF with a cause other than AMI.

We dichotomize the LDL research variable as optimal (<100 mg/dL) and non-optimal (>100 mg/dL), using an ordinal scale. The LDL cut-off value of 100 mg/dL was chosen based on the 2019 Indonesian Guidelines for the Management of Dyslipidemia.[6] The LDL cut-off value selected for this study was based on prior studies and clinical judgment.

Although the 100 mg/dL threshold was chosen for convenience, it is important to note that this value exceeds current clinical recommendations for

patients with AMI and HF. According to the 2018 American College of Cardiology/American Heart Association (ACC/AHA) and Indonesian Society of Endocrinology (Perkumpulan Endrokinologi Indonesia, PERKENI) guidelines, patients with AMI or HF are classified as very high risk, with an LDL target level of less than 70 mg/dL. Some recent guidelines even suggest an LDL target as low as 55 mg/dL. The 100 mg/dL cutoff value used in this study exceeds the recommended target; however, it was selected for practical reasons and based on available data.

This choice reflects the researcher's discretion in defining cutoff points based on available clinical evidence and data constraints.[8] Thus, we employed 100 mg/dL as a clinically relevant, evidence-based cutoff to categorize in our analysis. For HF in patients with AMI, we categorize the presence or absence of HF and report it in the form of a nominal variable.

We used RStudio software (RStudio, PBC, Boston, MA, USA)[9] to perform bivariate analysis between LDL level categories and the presence or absence of HF complications using Chi-square statistical analysis/Fisher's exact test, while for baseline characteristic analysis, we categorize based on the presence or absence of HF, and we analyze using SPSS software (IBM Corp., Armonk, NY, USA).[10]

A multivariate logistic regression analysis was performed using SPSS to examine the relationship between LDL levels and the incidence of HF in patients with AMI. The analysis was adjusted for potential confounding factors, including age, gender, comorbidities (e.g., hypertension, diabetes), and other variables. Statistical significance was determined at $p < 0.05$.

Results

The study population consisted of 97 patients with a mean age of 62.61 years (Standard Deviation [SD] 10.40) in the HF+ group and 63.60 years (SD 9.96) in the HF- group. Males dominated the gender distribution, comprising 73.1% of patients in the HF+ group and 26.9% in the HF- group. Regarding LDL levels, the mean value in the HF+ group was 143.61 mg/dL (SD 54.46), and in the HF- group, it was 72.68 mg/dL (SD 25.17). The population was divided into two groups: 72 patients in the HF+ group and 25 patients in the HF- group. In addition to age, gender, and LDL levels, other baseline characteristics, such as hypertension and diabetes, were evaluated. The detailed distribution of these characteristics is shown in Table 1.

Table 1. Baseline patient characteristics based on heart failure.

Variable	HF+ (N=72)	HF- (N=25)	P-value[2]
Age	62.61 (10.40)[1]	63.60 (9.96)[1]	0.467
Diagnosis			
NSTEMI	24 (80%)	6 (20.0%)	0.377
STEMI	48 (71.6%)	19 (28.4%)	
Diabetes			
Diabetes+	22 (73.3%)	8 (26.7%)	0.893
Diabetes-	50 (74.6%)	17 (25.4%)	
Hypertension			
Hypertension+	37 (74.0%)	13 (26.0%)	0.958
Hypertension-	35 (74.5%)	12 (25.5%)	
Systolic	137.68 (26.19)[1]	130.52 (38.91)[1]	0.011*
Diastolic	86.25 (16.28)[1]	79.92 (24.14)[1]	0.120
Heart Rate	87.86 (19.29)[1]	78.36 (21.99)[1]	0.217
Respiration Rate	23 (20.24)[2]	22 (20.24)[2]	0.929
Temperature	36.4 (36.2, 36.73)[2]	36.6 (36.3, 36.6)[2]	0.178
LDL	143.61 (54.46) [1]	72.68 (25.17)[1]	0.017*
LDL Level			
Non-Optimal	59 (95.2%)	3 (4.8%)	0.000***
Optimal	13 (37.1%)	22 (62.9%)	

HDL	38.5 (33.00, 51.25)[2]	43 (37.00, 54.00)[2]	0.644
TG	128.89 (46.87)[1]	126.40 (61.12)[1]	0.557
Gender			
Female	23 (76.7%)	7 (23.3%)	0.711
Male	49 (73.1%)	18 (26.9%)	
Smoking History			
Present	49 (73.1%)	18 (26.9%)	0.711
Absent	23 (76.7%)	7 (23.3%)	

[1]Mean (SD) [2]Median (Q1, Q3); n (%)
[2]*p<0.05; **p<0.01; ***p<0.001
Notes: HF: Heart Failure; NSTEMI: Non–ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; TG: Triglycerides.

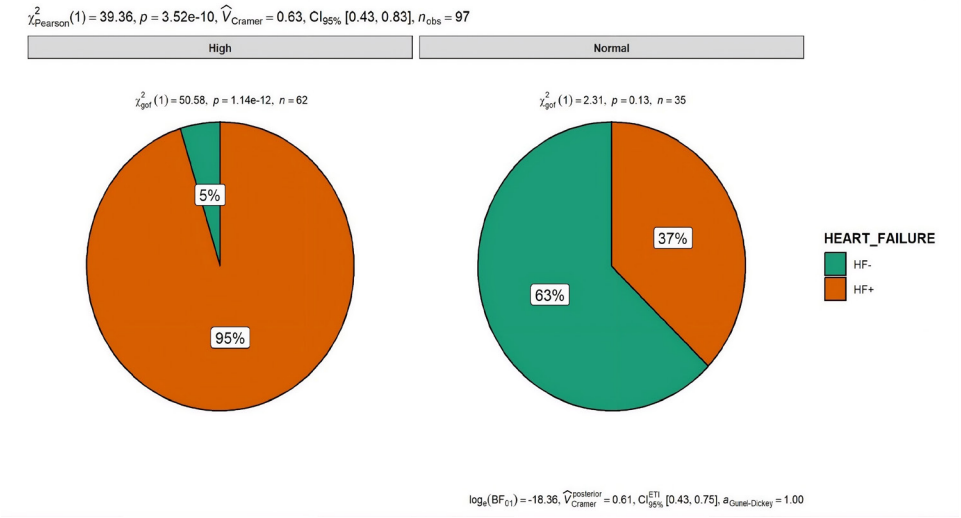

Figure 1. Bivariate analysis of association between LDL levels and heart failure.

In Figure 1, the analysis indicates a clear association between LDL levels and the incidence of HF. Among patients with high LDL levels, 95% developed HF, compared to only 37% of those with normal LDL levels. The association between high LDL levels and HF was statistically significant with a P-value <0.05, suggesting a strong link between elevated LDL levels and the increased risk of HF. On the other hand, individuals with normal LDL levels did not exhibit a significant association with HF (p = 0.13), as 63% of them did not develop HF. This indicates that while high LDL levels significantly contribute to HF incidence, normal LDL levels do not show the same effect. Overall, the findings reinforce the significant impact of high LDL levels on HF risk, while normal LDL levels have little influence.

Table 1 presents the baseline characteristics. The study population consisted of 97 patients, with a mean age of 62.61 years in the heart failure (HF+) group and 63.60 years in the non-heart failure (HF-) group, showing no significant difference in age (p = 0.467). The distribution of diagnoses showed no significant association between the type of diagnosis and the incidence of HF (p = 0.377), with 80% of the HF+ group diagnosed with NSTEMI and 28.4% of the HF- group diagnosed with STEMI. Regarding comorbidities, diabetes was present in 73.3% of the HF+ group and 26.7% of the HF- group, with no significant difference (p = 0.893). Hypertension affected 74% of the HF+ group and 26% of the HF- group (p = 0.958). Systolic Blood Pressure (SBP) differed significantly between the two groups (p = 0.011), with lower values in the HF- group. Diastolic Blood Pressure (DBP), heart rate, respiratory rate, and body temperature did not differ significantly between the two groups (p = 0.120, 0.217, 0.929, and 0.178, respectively). LDL levels were significantly higher in the HF+ group (mean 143.61 mg/dL) than in the HF- group (mean

72.68 mg/dL). Of the HF+ group, 95.2% had high LDL levels, which were strongly correlated with HF ($p = 0.000$). No significant differences were found in HDL levels, triglyceride levels, gender distribution, or smoking history between the two groups ($p = 0.644$, 0.557, 0.711, and 0.711, respectively).

After adjusting for other factors, multivariate logistic regression identified LDL levels as the only variable significantly associated with HF ($p < 0.001$; Table 2). The model demonstrated good overall performance and a strong fit to the data ($p = 0.804$), indicating reliable prediction of HF occurrence among patients with AMI. Higher LDL levels were strongly linked to an increased risk of HF, with each 1 mg/dL increase in LDL associated with a 6.9% higher probability of HF (odds ratio = 1.069, $p < 0.001$). In contrast, other clinical variables, such as age, blood pressure, diabetes, and hypertension, were not significantly associated ($p > 0.05$ for all). These findings suggest that elevated LDL is an independent and dominant predictor of HF in this population.

Discussion

In this study, we looked into the association between the occurrence of HF in individuals who had an AMI and their LDL cholesterol levels. Our main finding indicates that there is a substantial correlation between elevated or non-optimal LDL levels and a higher risk of HF incidence in this group of participants. Additionally, SBP was the only significant baseline characteristic independently associated with the development of HF. These results highlight the interplay between lipid metabolism and hemodynamic stress in post-AMI outcomes, with implications for risk stratification and management.

Our observation that elevated LDL levels correlate with HF incidence aligns with the understanding that dyslipidemia exacerbates ischemic injury and promotes adverse cardiac remodeling.[11] LDL cholesterol contributes to endothelial dysfunction, plaque instability, and microvascular obstruction during AMI, potentially extending infarct size and impairing left ventricular function. This mechanistic pathway is supported by several studies.

Table 2. Multivariate analysis result.

Variable	B	Standard Error (SE)	P-value (Sig.)	Odds Ratio
Age	-0.024	0.040	0.553	0.976
Diagnosis	-0.317	0.885	0.720	0.728
Diabetes	0.641	0.945	0.498	1.899
Hypertension	-0.846	1.233	0.493	0.429
Systole	0.017	0.027	0.516	1.018
Diastole	-0.008	0.035	0.828	0.992
HR	0.025	0.023	0.267	1.025
RR	0.093	0.129	0.469	1.098
Temperature	0.114	0.977	0.907	1.121
LDL	0.067	0.015	<.001	1.069
HDL	-0.016	0.033	0.621	0.984
Triglycerides	-0.010	0.008	0.236	0.990
Gender	0.143	0.889	0.872	1.154

HR: Heart Rate; RR: Respiration Rate; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein.

The CANTOS trial demonstrated that inflammatory pathways driven by atherosclerosis (where LDL is a key mediator) increase HF risk post-AMI.[12] Lowering LDL via targeted therapies reduced HF hospitalizations, underscoring LDL's role in post-infarct complications.[12-13]

The DYSIS II study highlights that individuals suffering from coronary heart disease, such as those with ACS, often present with high LDL cholesterol levels, and many do not meet the recommended target of LDL < 70 mg/dL. In addition, ACS patients have a very high cardiovascular risk, and greater LDL levels have been linked to worse clinical outcomes, such as an increased chance of developing HF. This finding is especially relevant.[14]

Adverse myocardial remodeling, or alterations in the size, shape, and function of the heart muscle, can result from high SBP, especially after an AMI. Increased SBP can worsen left ventricular dysfunction, increasing the likelihood of developing HF. Based on this data, high blood pressure is an established risk factor for HF, strokes, and other cardiovascular diseases.

In AMI patients, those with a history of hypertension are at higher risk of developing HF post-infarction, largely due to the combined effects of high blood pressure on myocardial function and vascular integrity. Studies mentioned in the article, like the GISSI-2 trial, found that hypertensive patients experienced higher mortality rates and worse clinical outcomes after AMI compared to those without hypertension.[15]

The CORONA trial[16] found no HF benefit from LDL lowering in chronic HF patients with ischemic etiology, suggesting that once HF is established, lipid modulation may not reverse remodeling. Contrary to the view from our study that elevated LDL cholesterol levels significantly contribute to HF development, in line with recent research, LDL might not directly contribute to the occurrence of HF, particularly in those who have experienced an AMI.

For instance, research indicates that in certain populations, elevated LDL levels may not significantly affect the development of HF, with other factors, such as blood pressure, infarct size, and comorbidities, being more predictive of HF outcomes.[17] Studies have shown that lowering LDL cholesterol with statin therapy does not always imply a significant reduction in HF. Incidence or mortality, suggesting that LDL levels alone may not be as pivotal in the development of HF as previously thought.[16]

A FOURIER trial sub-analysis noted that while LDL reduction prevented atherosclerotic events, HF risk reduction was less pronounced, implying alternative pathways (e.g., fibrosis, metabolic dysfunction) may dominate HF pathogenesis in stable CAD.[18]

Despite substantial evidence supporting the role of LDL in ischemic injury and adverse cardiac remodeling, recent studies, such as the CORONA and FOURIER trials[16,18], highlight that once HF is established, lipid modulation may have limited efficacy in reversing cardiac remodeling and reducing the incidence of HF.

One of the study's limitations is that the use of lipid-lowering medications, including statins, in the sample was not recorded and therefore not accounted for. To further strengthen the study's findings and reduce potential bias, future researchers should be more precise in identifying which individuals have received statins or other lipid-lowering medications and which have not. A limitation of this study is the use of 100 mg/dL as the LDL cutoff for patients with AMI. This cutoff value exceeds the current clinical guidelines' recommended LDL target of <70 mg/dL for very high-risk patients. Although the chosen cutoff value is based on prior studies and available data, it should be acknowledged that it exceeds the optimal LDL target for this population. This higher cutoff may limit the generalizability of the findings to clinical practice, particularly for cardiovascular risk management.

Future studies may consider using the recommended LDL targets to align with the current guidelines. Another limitations of our study include the observational design, potential confounding factors, and the need for longer follow-up to assess long-term outcomes. Further randomized controlled trials are necessary to more definitively clarify the role of LDL reduction in preventing HF in post-AMI patients and to explore the interplay between lipid metabolism, blood pressure, and myocardial remodeling in this high-risk population.

Conclusion

In conclusion, this investigation discovered a strong association between elevated LDL levels and the increased incidence of HF in AMI patients, with SBP also playing a crucial role. These results highlight the importance of managing both lipid levels and blood pressure in patients with AMI.

List of Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
DBP	Diastolic Blood Pressure
HDL	High-Density Lipoprotein
HF	Heart Failure
HR	Heart Rate
ICU	Intensive Care Unit
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
MI	Myocardial Infarction
NSTEMI	Non–ST-segment Elevation Myocardial Infarction
PERKENI	Indonesian Society of Endocrinology
ROS	Reactive Oxygen Species
RR	Respiratory Rate
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SD	Standard Deviation
STEMI	ST-segment Elevation Myocardial Infarction

Ethical Clearance

This study has received ethical approval from the Chair of the Health Research Ethics Committee at RSI Purwokerto No. No. 27/ND/KEPK/RSIP/XI/2024.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

Ghossan Faisol contributed to the conception and design of the study. Ensuring the consistency and coherence of the theoretical framework was also his responsibility, as was performing the data analysis and interpretation and drafting the manuscript. Sofina Kusnadi, Joriandhita Surya Ramadhan, and Erdiansyah Zulyadaini served as subject matter experts, critically reviewing the manuscript to ensure conceptual accuracy, theoretical consistency, and intellectual coherence, as well as revising it for important intellectual content.

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Conflict of Interest

None.

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Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that they did not use generative artificial intelligence (AI) or AIassisted technologies in writing, editing, or preparing this manuscript. The authors conducted all aspects of the manuscript, including conceptualization, data composition, solely.

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Original Article

Excessive Polypharmacy Among Indonesian Heart Failure Patients: Clinical Correlates and Care Implications

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Abstract

Background: Heart Failure (HF) is a major global health problem that often coexists with multiple chronic comorbidities, requiring complex pharmacotherapy. The use of numerous concurrent medications increases the risk of polypharmacy and excessive polypharmacy, which may lead to adverse drug reactions, drug–drug interactions, poor adherence, and higher healthcare utilization. Despite growing awareness of this issue, evidence on the prevalence and determinants of excessive polypharmacy among Indonesian HF patients remains scarce.

Methods: This single-center cross-sectional sub-analysis was derived from a cross-sectional study involving 494 adult HF patients treated at Hasna Medika Cardiovascular Hospital, Cirebon, between January and December 2023. HF diagnosis was confirmed by cardiologists using the European Society of Cardiology (ESC) criteria. Polypharmacy was defined as the use of ≥7 medications, while excessive polypharmacy was defined as ≥10 medications. Clinical and demographic variables were extracted from Electronic Medical Records (EMR). Bivariate analysis was performed using Chi-square or Fisher's exact tests, followed by multivariate logistic regression to identify independent determinants of excessive polypharmacy.

Results: The mean age of participants was 58.1 ± 10.5 years, and 53.4% were male. Overall, 42.5% of patients met the criteria for polypharmacy, and 15.6% (n=77) met the criteria for excessive polypharmacy. The most frequent comorbidities were Coronary Artery Disease (CAD) (80.2%), hypertension (23.1%), and Type 2 Diabetes Mellitus (T2DM, 20.0%). In multivariate analysis, T2DM (Adjusted Odds Ratio [AOR] 17.21, 95% CI 8.39–35.34), Chronic Kidney Disease (CKD) (AOR 5.97, 95% CI 2.37–15.03), Chronic Obstructive Pulmonary Disease (COPD) (AOR 6.64, 95% CI 2.64–16.69), and asthma (AOR 26.32, 95% CI 5.79–119.67) were identified as independent determinants of excessive polypharmacy. The model demonstrated good fit (McFadden pseudo-R^2 = 0.351; Hosmer–Lemeshow p = 0.62).

Conclusions: Excessive medication burden is common among HF patients, particularly among those with metabolic and pulmonary comorbidities. These findings highlight the need for systematic medication review and rational prescribing strategies while recognizing that higher medication counts do not necessarily indicate inappropriate prescribing.

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Keywords: Cardiovascular Pharmacotherapy, Heart Failure, Polypharmacy

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Introduction

Heart Failure (HF) is a severe, progressive condition where the heart struggles to pump enough blood to meet the body's demands for oxygen and nutrients. It represents the advanced stage of various heart conditions, such as Coronary Artery Disease (CAD), high blood pressure, and cardiomyopathies. HF is a growing global health concern, impacting an estimated 64 million people worldwide, and its incidence and prevalence are rising despite medical advancements.[1-5] This disease creates significant economic and healthcare challenges due to frequent hospitalizations, lost productivity, and high long-term care expenses. In many regions, HF accounts for 1-2% of total healthcare spending, highlighting its substantial impact on patients and health systems.

Globally, HF affects 1-2% of adults, with prevalence sharply increasing to over 10% in individuals over 70. In Asia, recent data indicate an Age-Standardized Prevalence Rate (ASR) of roughly 722.5 per 100,000 people, with Southeast Asian nations showing a consistent upward trend.[2-3] The situation in Indonesia is particularly worrying, with an estimated ASR of 900.9 per 100,000, which is considerably higher than in many neighboring Southeast Asian countries.[6] Additionally, Indonesia reports higher one-year mortality rates, suggesting issues with disease recognition, limited access to effective treatments, and inconsistent application of clinical guidelines. These findings emphasize the urgent need to enhance HF management strategies in Indonesia through improved diagnosis, standardized treatment, and integrated chronic care. Effective HF treatment involves a comprehensive approach that combines medications, lifestyle changes, and device-based therapies. For patients with Heart Failure with reduced Ejection Fraction (HFrEF), the "four pillars of therapy"—β-blockers, Angiotensin-Converting Enzyme Inhibitor (ACEi) or Angiotensin Receptor Blocker (ARBs) (or Angiotensin Receptor–Neprilysin Inhibitor [ARNIs]), Mineralocorticoid Receptor Antagonists (MRA), and Sodium–Glucose Cotransporter 2 (SGLT2) inhibitors—are proven to decrease both illness and death.[7] However, HF rarely occurs in isolation. It is common for patients to have multiple chronic conditions, such as Type 2 Diabetes Mellitus (T2DM), Chronic Kidney Disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), hypertension, and Atrial Fibrillation (AF).[8-9]

Each of these co-existing conditions requires specific medications, leading to polypharmacy, which is the concurrent use of multiple drugs. The role of polypharmacy in HF is intricate. On the one hand, using multiple medications may be appropriate, reflecting guideline-directed medical therapy targeting distinct disease mechanisms. On the other hand, excessive or poorly coordinated polypharmacy increases risks such as adverse drug reactions, drug–drug and drug–disease interactions, poor adherence, and redundant therapies.[10-12] The threshold for defining polypharmacy varies considerably across studies. While the use of ≥5 medications is commonly adopted in general populations, this threshold may overestimate inappropriate medication burden in HF populations because guideline-directed medical therapy alone frequently requires multiple concurrent agents. Therefore, thresholds of ≥7 medications for polypharmacy and ≥10 medications for excessive polypharmacy were prespecified based on previous HF-specific and multimorbidity literature, aiming to better distinguish expected therapeutic complexity from excessive medication burden. Given the high prevalence of multiple comorbidities in HF, distinguishing between necessary and excessive medication use is vital for improving patient outcomes.

International registry data, including those from the ESC-HF Long-Term Registry, CHAMP-HF, and Asian-HF Registry, have shown high rates of polypharmacy among HF patients, especially those with cardio–renal–metabolic comorbidities.[13] However, data from Indonesia are scarce, with no previous studies comprehensively detailing the extent, composition, and factors contributing to excessive polypharmacy in local HF populations. This knowledge gap hinders clinicians and policymakers from implementing rational prescribing and deprescribing strategies tailored to the Indonesian healthcare system.

Against this backdrop, the Cirebon Heart Failure Cohort offers a unique opportunity to examine real-world medication patterns and quantify the burden of polypharmacy in a representative Indonesian population.[14] This sub-analysis, utilizing detailed Electronic Medical Record (EMR) data from a tertiary cardiovascular referral center, aims to identify clinical factors and comorbidities linked to excessive polypharmacy (≥10 medications) among HF patients.

Methods

Study Design

This study is a sub-analysis of a cross-sectional observational study conducted at Hasna Medika Cardiovascular Hospital, a tertiary referral center specializing in cardiovascular diseases in Cirebon, West Java, Indonesia. The hospital serves both urban and peri-urban populations across the Cirebon region, providing a representative overview of real-world HF management in a mixed healthcare setting. Data were obtained from the hospital's EMR system, which comprehensively documents patient demographics, clinical diagnoses, echocardiographic parameters, comorbidities, and medication prescriptions. Data collection covered all outpatient visits between January 1 and December 31, 2023, ensuring a complete annual representation of HF cases managed in the tertiary outpatient setting. The previous study aimed to describe the demographic, clinical, and pharmacologic characteristics of HF patients in Cirebon, while this sub-analysis specifically focused on evaluating the determinants of excessive polypharmacy among these patients.

Study Population and Sampling

The study population included all adult patients aged ≥18 years with a confirmed diagnosis of HF, as established by treating cardiologists based on clinical presentation, diagnostic work-up, and echocardiographic findings consistent with the European Society of Cardiology (ESC) guidelines for HF diagnosis. Only patients with complete clinical and medication documentation were eligible. A total sampling method was used to include all eligible patients who met the inclusion criteria during the study period. Patients were excluded if medication records were incomplete or unclear, if they were hospitalized or undergoing acute treatment at the time of data abstraction, or if the HF diagnosis could not be confirmed by echocardiographic criteria. After applying these criteria, a final sample of 494 patients was included for analysis. This sample size was deemed adequate to provide sufficient statistical power to detect associations between comorbidities and excessive polypharmacy, based on logistic regression analysis.

Study Definitions

HF subtypes were categorized based on Left Ventricular Ejection Fraction (LVEF) as follows: HFrEF with LVEF ≤40%, HFmrEF (Heart Failure with Mildly Reduced Ejection Fraction) with LVEF 41–49%, and HFpEF (Heart Failure with Preserved Ejection Fraction) with LVEF ≥50%.[11] Polypharmacy was defined as the concurrent use of ≥7 medications, while excessive polypharmacy referred to ≥10 medications. These thresholds were prespecified prior to analysis based on previous literature evaluating medication burden in HF populations where standard guideline-directed therapy frequently requires multiple concurrent medications.[10]

Comorbidities were defined as physician-documented chronic medical conditions recorded in the EMR. These included, but were not limited to, CAD, T2DM, CKD, COPD, asthma, hypertension, dyslipidemia, AF, cerebrovascular disease, and Chronic Venous Insufficiency (CVI). Prescribed drugs were grouped into pharmacological classes according to the Anatomical Therapeutic Chemical (ATC) classification system (e.g., beta-blockers, ACEi/ARB/ARNI, MRAs, loop diuretics, antiplatelets, antihyperglycemics, and respiratory agents). Fixed-dose combinations were counted as a single medication when prescribed as a single formulation.

Data Management and Quality Control

Data extraction was performed by two trained research assistants under the supervision of the principal investigator (YPR). Random checks and cross-validation of 10% of entries were conducted to ensure accuracy and consistency. Incomplete or inconsistent entries were verified against original patient charts before final inclusion. To maintain data integrity, double-entry verification was applied during database creation.

Statistical Analysis

Data were analyzed using Stata version 17.0. Continuous variables were summarized as means ± Standard Deviations (SD) for normally distributed data, or as medians with Interquartile Ranges (IQR) for skewed distributions. Categorical variables were presented as frequencies and percentages. Associations between excessive polypharmacy

(dependent variable) and independent variables (age, sex, comorbidities, and Ejection Fraction [EF] category) were first explored using the Chi-square test or Fisher's exact test, as appropriate. Variables were initially screened using bivariate analyses. Variables with p-values <0.25, together with clinically relevant variables identified a priori (including age, sex, HF phenotype, CAD, hypertension, AF, Percutaneous Coronary Intervention (PCI) history, and comorbidity burden), were considered during multivariable model construction. Final covariate selection was based on clinical relevance, model stability, and avoidance of multicollinearity.

A multivariate logistic regression model was used to identify independent determinants of excessive polypharmacy (≥10 drugs). Results were reported as Adjusted Odds Ratios (AORs) with 95% confidence intervals (CIs). Model fit was assessed using McFadden's pseudo-R^2 and the Akaike Information Criterion (AIC). The Hosmer–Lemeshow goodness-of-fit test was applied to evaluate model calibration. Statistical significance was defined as $p < 0.05$ (two-tailed). All analyses were designed to identify clinically meaningful determinants of excessive medication use and to support the development of rational prescribing strategies in the HF population.

Ethical Approval

Ethical approval was obtained from the Research Ethics Committee of Gunung Jati General Hospital (No. 060/LAIKETIK/KEPPKRSGJ/X/2024). All patient data were anonymized.

Results

A total of 494 patients with clinically confirmed HF were included in the analysis. The mean age of the cohort was 58.1 ± 10.5 years (range 27–86 years), and 53.4% (n = 264) were male. Age distribution showed that almost half of the sample were middle-aged adults (45–59 years, 46.0%), while 40.1% were aged 60–74 years; patients aged ≥75 years represented 5.1% of the population. LVEF categories were relatively evenly represented: 35.0% had HFrEF, 31.8% had HFmrEF, and 33.2% had HFpEF (Table 1). Comorbid conditions were common and contributed substantially to treatment complexity. CAD was present in 80.2% of patients, hypertension in 23.1%, and T2DM in 20.0%. Less frequent but clinically relevant comorbidities included CKD (7.7%), COPD (8.9%), AF (14.4%), CVI (7.3%), stroke (2.2%), asthma (2.0%), and dyslipidemia (2.8%). Overall, 171 patients (34.6%) had three or more documented comorbidities, indicating a substantial burden of multimorbidity within this tertiary referral population (Figure 1).

The mean number of prescribed medications per patient was 6.82 ± 2.66 (range 2–16), with a modal value of five drugs. When applying prespecified thresholds, 42.5% of patients (n = 210) met the study definition of polypharmacy (≥7 drugs), and 15.6% of the total cohort (n = 77) met criteria for excessive polypharmacy (≥10 drugs). Among patients meeting the excessive polypharmacy definition, the median number of drugs was 11 (IQR 10–13), highlighting

Table 1. Baseline characteristics of heart failure patients (n=494).

Sample Characteristic	n	%
Sex		
Male	264	53.4
Female	230	46.6
Age group (mean age ± SD)	58.1 ± 10.48	
18–44	44	8.9
45–59	227	46.0
60–74	198	40.1
≥75	25	5.1
Number of medications (mean ± SD)	6.82 ± 2.66	
≤4 drugs	75	15.2
5 drugs	115	23.3
6 drugs	94	19.0
≥7 drugs (polypharmacy)	210	42.5
Comorbidities		
<3	323	65.5
≥3	171	34.6

HF Classification		
HFrEF (≤40%)	173	35.0
HFmrEF (41–49%)	157	31.8
HFpEF (≥50%)	164	33.2
History of PCI (yes)	103	20.9

HF:Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HFmrEF: Heart Failure with Mildly Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; PCI: Percutaneous Coronary Intervention.

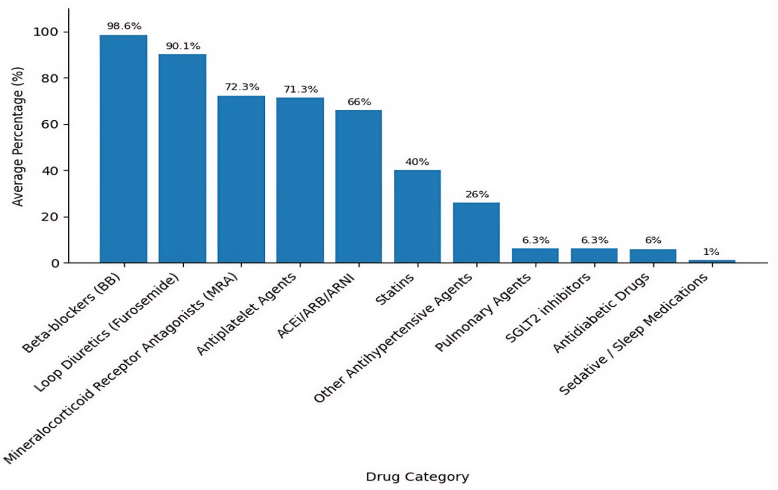

Figure 1. Proportion of prescribed medication classes among heart failure patients (n=494).

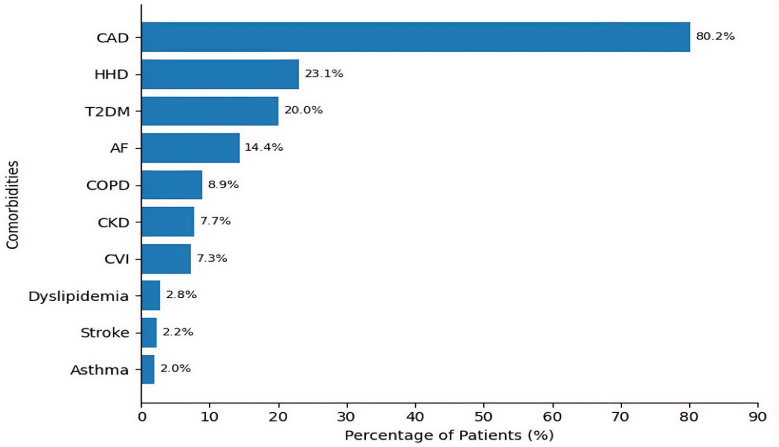

Figure 2. Distribution of comorbidities among heart failure patients (n=494).

a subgroup exposed to very high treatment intensity. Distribution by discrete medication counts showed 15.2% of patients received ≤4 drugs, 23.3% received 5 drugs, and 19.0% received 6 drugs, reinforcing that the medication burden was concentrated in a substantial minority of patients.

Analysis of drug classes revealed that guideline-directed HF therapies were commonly prescribed: beta-blockers were used by 98.6% of patients, loop diuretics (predominantly furosemide) by 90.1%, and mineralocorticoid receptor antagonists by 72.3%. Aspirin or other antiplatelet agents were used in 71.3%, and ACEi/ARBs/ARNIs in 66.0% of patients (Figure 2). Despite strong evidence for their benefit in contemporary HF care, SGLT2 inhibitors were prescribed to only 6.3% of patients, indicating limited uptake in this setting. Among patients with diabetes, metformin (4.1% of the entire cohort) and glimepiride (3.9%) were the most frequently recorded antihyperglycemic agents. Respiratory therapies were less prevalent overall but concentrated among those with pulmonary comorbidity; salbutamol inhalation was recorded in 4.3% and ipratropium bromide in 2.8% of the cohort.

Univariate comparisons demonstrated that age 45–59 years, having ≥3 comorbidities, T2DM, CAD, CKD, COPD, asthma, and prior PCI were significantly associated with polypharmacy ($p < 0.05$ for each). There was no statistically significant association between polypharmacy and sex or EF category in bivariate testing (sex $p = 0.48$; EF category $p = 0.21$). Given these findings, variables with $p < 0.25$ in bivariate screening were entered into multivariate logistic regression to identify independent determinants of excessive polypharmacy (≥10 drugs).

In multivariate logistic regression analysis, four comorbid conditions emerged as strong independent predictors of excessive polypharmacy. T2DM was associated with the greatest adjusted odds (AOR 17.21, 95% CI 8.39–35.34; $p < 0.001$), indicating that diabetic patients were markedly more likely to receive 10 or more medications compared with non-diabetic patients. CKD was independently associated with excessive polypharmacy with an AOR of 5.97 (95% CI 2.37–15.03; $p < 0.001$). Pulmonary comorbidities also had large effect sizes: COPD (AOR 6.64; 95% CI 2.64–16.69; $p < 0.001$) and asthma (AOR 26.32; 95% CI 5.79–119.67; $p < 0.001$) were both strongly associated with excessive medication burden (Table 2). Although patients with ≥3 comorbidities showed a directionally increased odds of excessive polypharmacy (AOR 1.90), this association did not reach conventional statistical significance (95% CI 0.96–3.77; $p = 0.067$), suggesting that the type of comorbidity is a more powerful driver of medication burden than comorbidity count alone. However, the large effect estimates and wide confidence intervals, particularly for asthma, should be interpreted cautiously because relatively small subgroup sizes may introduce sparse-data effects and model instability.

Table 2. Determinants of excessive polypharmacy (Multivariate logistic regression analysis).

Variable	AOR	95% CI	p-value
T2DM	17.21	8.39 – 35.34	<0.001
CKD	5.97	2.37 – 15.03	<0.001
COPD	6.64	2.64 – 16.69	<0.001
Asthma	26.32	5.79 – 119.67	<0.001
≥3 Comorbidities	1.90	0.96 – 3.77	0.067

AOR: Adjusted Odds Ratio; CI: Confidence Interval T2DM: Type 2 Diabetes Mellitus; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease.

Table 3. Fit model test.

Analysis	Value
McFadden's pseudo-R^2	0.351
AIC	289.53
Hosmer–Lemeshow	0.62

AIC: Akaike Information Criteria.

The model exhibited good explanatory capacity and adequate calibration. McFadden's pseudo-R^2 was 0.351, indicating that the included predictors accounted for a substantial proportion of the variance in excessive polypharmacy. The AIC for the model was 289.53, and the Hosmer–Lemeshow goodness-of-fit test indicated satisfactory calibration ($p = 0.62$) (Table 3). Mean medication counts differed markedly across clinically relevant subgroups. Patients with T2DM had a mean medication count of 10.9 ± 2.7 compared with 6.1 ± 2.3 among non-diabetic patients ($p < 0.001$). Those with CKD had a mean of 9.4 ± 3.1 drugs, and patients with COPD or asthma averaged 10.7 ± 2.8 drugs. When patients were dichotomized by comorbidity burden, those with ≥3 comorbidities received a mean of 9.5 ± 2.8 medications, compared with 5.3 ± 1.9 in those with fewer than 3 comorbidities ($p < 0.001$). These descriptive comparisons reinforce the multivariable findings that cardio–renal–metabolic and pulmonary conditions are associated with substantially greater medication exposure.

Discussion

This sub-analysis reveals that excessive polypharmacy is highly common among HF patients in Indonesian tertiary care settings, particularly those with co-occurring conditions like T2DM, CKD, COPD, and asthma. These results highlight

that the type and pathophysiological nature of comorbidities, rather than simply their number, are the primary factors driving the medication burden. This observation aligns with international registry data showing the significant role of the cardio–renal–metabolic axis in shaping the complexity of HF pharmacotherapy. The presence of multiple chronic diseases necessitates overlapping, often interacting treatments aimed at metabolic control, renal protection, and cardiovascular prevention.[15]

The notably high AOR for T2DM found in this study likely reflects the combined impact of multi-drug regimens that include both glucose-lowering and cardioprotective agents. HF patients with diabetes often require combinations of medications, including metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and, increasingly, SGLT2 inhibitors, in addition to the four fundamental HF drugs (beta-blockers, ACEi/ARB/ARNI, MRAs, SGLT2 inhibitors). These overlapping treatment areas increase the number of medications and raise the risk of drug–drug interactions and adherence challenges. The relatively low utilization of SGLT2 inhibitors despite their established benefits across the cardio–renal–metabolic continuum likely reflects ongoing barriers, including cost, availability, reimbursement limitations, and delayed implementation within routine practice. Previous studies, including the CHAMP-HF registry and the QUALIFY study, similarly reported that diabetic HF patients receive significantly more prescriptions than non-diabetic patients, primarily due to cardiometabolic overlap.[16]

In patients with CKD, excessive polypharmacy is partly explained by the need for additional medications to correct electrolyte imbalances, manage uremic symptoms, and prevent anemia progression. Drugs such as phosphate binders, potassium regulators, erythropoiesis-stimulating agents, and bicarbonate supplements are frequently co-prescribed. However, CKD also restricts the use or dosage adjustment of crucial HF drugs like ACEi/ARBs, MRAs, and ARNIs due to the risk of hyperkalemia and worsening renal function. This dual therapeutic challenge—requiring more drugs while limiting standard HF therapies—is a defining characteristic of the cardio–renal syndrome, a concept gaining recognition in both European and Asian HF populations.[17] The intricate balance between therapeutic effectiveness and renal safety significantly contributes to the excessive polypharmacy observed in this patient group.

Pulmonary comorbidities like COPD and asthma further exacerbate the pharmacological burden. Their co-occurrence with HF is frequent, given shared risk factors such as smoking, aging, and systemic inflammation. Management typically involves multiple inhaled bronchodilators (β_2-agonists, antimuscarinics), inhaled corticosteroids, and sometimes systemic corticosteroids or antibiotics for exacerbations. These medications can interact unfavorably with HF treatments—β-agonists can worsen tachycardia and arrhythmias, corticosteroids may cause fluid retention and aggravate HF symptoms, and certain antibiotics (e.g., macrolides) can prolong QT intervals.[18] This interaction creates a therapeutic dilemma that calls for individualized and multidisciplinary management, ideally involving cardiologists, pulmonologists, and pharmacists.

Within the Indonesian healthcare context, structural and systemic factors likely heighten the risk of excessive polypharmacy. Fragmented care delivery between hospitals and primary care, limited medication formularies, and inconsistent adherence to evidence-based guidelines contribute to overlapping or redundant prescriptions. For instance, the low adoption of SGLT2 inhibitors and ARNIs in Indonesia—despite their proven benefits in both HFrEF and HFpEF—points to ongoing challenges in accessibility, cost, and clinician familiarity.[19] Addressing these obstacles requires not only education and system integration but also policy reforms to include newer, guideline-directed medical therapies in national formularies and insurance coverage. Disease severity may substantially influence medication burden in HF populations. Variables such as New York Heart Association (NYHA) functional class, duration of HF, history of hospitalization, severity of renal function, natriuretic peptide levels, and continuous LVEF measurements may influence prescribing intensity and medication burden. Unfortunately, these variables were not fully available in the EMR system and therefore could not be analyzed.

An additional finding worth highlighting is the relatively lower utilization of ACEi/ARB/ARNI compared with beta-blockers and MRAs. Several explanations may contribute to this pattern. First, the presence of CKD and concerns regarding worsening renal function or hyperkalemia may limit prescription or dose optimization of renin–angiotensin system inhibitors.[20] Second, financial barriers and limited formulary availability may restrict access to newer agents such as ARNIs in routine clinical practice. Finally, real-world prescribing

inertia and physician preference may contribute to differential adoption of guideline-directed therapies within resource-limited healthcare systems.

Furthermore, this study reinforces the concept of the cardio–renal–metabolic continuum, which acknowledges the interconnected pathophysiology of heart, kidney, and metabolic disorders.[21-22] The emergence of SGLT2 inhibitors as a class of drugs with diverse benefits—improving cardiovascular outcomes, reducing HF hospitalization, and slowing CKD progression—represents a significant shift from symptom management to disease modification.[23-24] However, incorporating these therapies into already complex regimens demands precision and careful monitoring to prevent therapeutic duplication or unnecessary polypharmacy. Therefore, the rationalization of pharmacotherapy should aim to maximize disease-modifying drugs while minimizing redundant symptomatic agents.[25-29]

The international perspective offers valuable context. The ESC-HF-LT registry, CHAMP-HF registry, and Japanese CHART-2 cohort all reported average medication counts of 9-12 among HF patients with multiple comorbidities.[29-31] Our findings align with these trends, indicating that the burden of polypharmacy in HF is a universal issue, irrespective of the healthcare system. Nevertheless, in low- and middle-income countries like Indonesia, the consequences might be more severe due to limited resources, varying medication adherence, and limited integration of pharmacists into outpatient care.[32]

Strengths and Limitations

This study has several notable strengths. It is one of the first investigations in Indonesia to systematically quantify the prevalence and determinants of excessive polypharmacy among HF patients using a clinically verified cohort with comprehensive medication documentation. The use of real-world data extracted from EMR enhances the validity and applicability of the findings to current clinical practice. Furthermore, the application of multivariate logistic regression analysis provides robust identification of independent predictors of excessive polypharmacy, minimizing confounding effects from demographic and comorbidity-related variables.

Nevertheless, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference regarding the temporal relationship between comorbidities and the development of excessive polypharmacy. Future longitudinal or prospective studies are needed to determine whether polypharmacy directly contributes to adverse clinical outcomes, such as hospitalization, medication non-adherence, or mortality. Second, this study was conducted at a tertiary cardiovascular referral center; the patient population was predominantly composed of individuals with CAD and complex cardiovascular conditions. Therefore, referral bias may exist, and the medication burden observed in this cohort may not fully represent community-based or primary care HF populations. Despite these limitations, the study provides an essential early framework for understanding the multidimensional determinants of excessive polypharmacy in HF within an Indonesian healthcare context. It establishes a basis for future multicenter, longitudinal, and interventional studies aimed at evaluating deprescribing strategies, clinical outcomes, and the cost-effectiveness of integrated polypharmacy management programs.

Conclusion

Excessive polypharmacy is highly prevalent among HF patients in Indonesia, especially in those with comorbidities such as T2DM, CKD, COPD, and asthma. These findings highlight that medication burden in HF is driven not merely by the number of coexisting conditions, but by the complexity and interdependence of cardio–renal–metabolic and pulmonary comorbidities. The coexistence of these systemic disorders results in overlapping pharmacological domains, leading to extensive and often challenging medication regimens.

List of Abbreviations

ACEi	Angiotensin-Converting Enzyme Inhibitor
AF	Atrial Fibrillation
AIC	Akaike Information Criterion
AOR	Adjusted Odds Ratio
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
ASR	Age-Standardized Prevalence Rate
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CVI	Chronic Venous Insufficiency
EF	Ejection Fraction
EMR	Electronic Medical Record
ESC	European Society of Cardiology

HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
IQR	Interquartile Range
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonist
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
SD	Standard Deviation
SGLT2	Sodium–Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus

Ethical Clearance

Ethical approval was obtained from the Research Ethics Committee of Gunung Jati General Hospital (No. 060/LAIKETIK/KEPPKRSGJ/X/2024). All patient data were anonymized.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

YPR: conceptualized and designed the study, curated and analyzed the data, interpreted the findings, and drafted the manuscript. WP: contributed to study design, data interpretation, critical review of the manuscript, and refinement of the discussion and conclusions. BBS: provided senior supervision, methodological guidance, and critical revisions for important intellectual content. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Availability of Data and Materials

The analysis data and anonymous data samples are held by the corresponding author and may be accessed with special permission for research purposes.

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Original Article

A Comparative Study of sFt-1 and Prolactin Levels in Peripartum Cardiomyopathy Patients With and Without Preeclampsia

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Abstract

Background: Peripartum Cardiomyopathy (PPCM) is a type of heart failure that occurs from late pregnancy to the early postpartum period. While the exact etiology of PPCM remains unclear, several risk factors, including preeclampsia, have been identified. It is hypothesized that PPCM with and without preeclampsia may involve distinct pathophysiological mechanisms, which could be reflected in differences in biomarker levels. This study aims to explore this hypothesis by comparing prolactin levels between PPCM patients with and without preeclampsia.

Methods: This observational analytical study employed a cross-sectional design. The study population consisted of PPCM patients registered at Dr. Hasan Sadikin Hospital, Bandung, from September 2018 to June 2024. Subjects were classified into two groups: PPCM with preeclampsia and PPCM without preeclampsia. Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) and prolactin levels were measured at the time of PPCM diagnosis.

Results: A total of 66 patients were included in the final analysis (43 with PPCM and preeclampsia and 23 without preeclampsia). Patients with PPCM and preeclampsia had higher sFlt-1 levels than patients with PPCM without preeclampsia (128.1 [Interquartile Range (IQR) 90.8–279.5] vs. 94.9 [IQR 82.7–110.6] pg/ml; p = 0.046), while prolactin levels did not differ significantly between two groups (36.52 [15.59–88.58] vs. 22.11 [12.69–44.25] ng/ml; p = 0.176). In the PPCM group with preeclampsia, 44.2% (p = 0.002) of patients had elevated levels of both sFlt-1 and prolactin, while none of the subjects without preeclampsia exhibited this combination.

Conclusions: sFlt-1 levels are higher in PPCM with preeclampsia, whereas prolactin levels do not differ significantly between the two groups.

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Keywords: Peripartum cardiomyopathy, Preeclampsia, Prolactin, Soluble fms-like tyrosine kinase 1, Vasoinhibin

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Introduction

Peripartum Cardiomyopathy (PPCM) is a type of heart failure that occurs during the last trimester of pregnancy, during the period leading up to childbirth, or during the early postpartum period. The incidence rate and clinical outcomes of PPCM vary by region.[1] The global prevalence of PPCM varies by geographic area. For instance, PPCM occurs at a rate of one in 96 births in Nigeria, whereas in Japan, it occurs at a rate of one in 20,000 births.[1] At Dr. Soetomo Hospital Surabaya, PPCM occurs at a rate of one in 149 live births.[2]

The exact cause of PPCM is still unknown. However, an imbalance between proangiogenic factors, such as Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF), and antiangiogenic factors, such as Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1), contributes to the development of this condition.[3] Various risk factors have been identified, one of which is preeclampsia. Preeclampsia is reported to occur in approximately 22% of patients with PPCM.[4]

In the pathogenesis of PPCM, the "two-hit" model is used. This model involves sFlt-1 and prolactin, which play a role in disrupting the angiogenic balance during pregnancy. Levels of sFlt-1 have been extensively studied and have been shown to increase in cases of preeclampsia. The sFlt-1/PlGF ratio can be used to accurately distinguish preeclampsia from a normal pregnancy. Increased sFlt-1 levels in patients with preeclampsia reflect an angiogenic imbalance that contributes to the development of the condition.[3] In PPCM, elevated sFlt-1 levels have been linked to poorer heart remodeling and a higher New York Heart Association (NYHA) functional class, as reported in the Investigation in Pregnancy Associated Cardiomyopathy (IPAC) study.[2] Additionally, elevated prolactin levels can negatively affect the heart by inhibiting nitric oxide synthase and causing endothelial damage, thereby interfering with angiogenesis.[5]

Patients with PPCM, whether or not they have preeclampsia, exhibit similar cardiomyopathy phenotypes. However, the pathogenesis of the two conditions may differ. To date, no studies have compared sFlt-1 and prolactin levels in PPCM patients with and without preeclampsia. This study aims to address this gap by measuring and comparing sFlt-1 and prolactin levels in both groups, and evaluating their implications for PPCM pathogenesis and therapy. Understanding the pathophysiology of PPCM is important for developing more effective, targeted therapies and for determining whether PPCM, with or without preeclampsia, is the same disease or a different one.

Methods

Cohort

This study focused on patients with PPCM. The research subjects were registered in the Long-Term Registry on Patients with PPCM at Dr. Hasan Sadikin Hospital in Bandung from August 2018 to June 2024. Eligible patients were women diagnosed with PPCM who had blood samples taken at the time of initial diagnosis. Patients with chronic kidney disease, type 2 diabetes mellitus, inappropriate blood samples, or incomplete blood collection data were excluded from the analysis. Subjects were grouped based on clinical status into those with PPCM accompanied by preeclampsia and those without. Of the 66 patients who met the criteria, 43 had PPCM with preeclampsia, and 23 had PPCM without preeclampsia.

Research Protocol

This is an analytical, observational study with a cross-sectional design, followed by an analysis of unpaired numerical comparative tests. Sampling was performed using the total sampling method on the population of PPCM patients registered in the long-term registry of patients with PPCM at Dr. Hasan Sadikin Hospital in Bandung from September 2018 to June 2024. Data were collected retrospectively from the PPCM registry using medical record data.

Blood Sampling and Biomarker Analysis

Peripheral venous blood collection of 3 mL was performed via the cubital vein by trained health workers at the time of the patient's first diagnosis of PPCM. The sample was stored at 4°C and sent to the Clinical Pathology Laboratory at Dr. Hasan Sadikin Hospital in Bandung within two hours. The plasma was separated via centrifugation at 1000×g for 20 minutes at 2–8°C and then stored at −80°C until examination. Once the minimum sample count is met, sFlt-1 and prolactin levels are checked simultaneously. This test measures the concentration of sFlt-1 and prolactin in plasma.

Statistical Analysis

Data processing and analysis were carried out using IBM SPSS Statistics version 24.0. The Shapiro–Wilk test was used to test the distribution of numerical data. Data with a normal distribution is presented as mean values and standard deviations, while data without a normal distribution is presented as the median and range. Categorical data is presented

as numbers and percentages. Comparisons between the two groups were made using an unpaired t-test or a Mann–Whitney U-test for numerical variables and a chi-square test or a Fisher's exact test for categorical variables. All statistical tests used a significance level of $p < 0.05$.

Results

The demographic characteristics, obstetric status, and early clinical status of the subjects were divided into two categories: PPCM with and without preeclampsia.

Table 1. Subject characteristics research.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia
	n=43	n=23
Demographics		
Age (years), mean ± SD	31.7 ± 7.9	27.1 ± 6.7
BMI (kg/m^2), median (min-max)	26 (16.9 – 44.5)	22.2 (18.2 – 36.4)
Education Level, (n, %)		
Elementary School	6 (14)	1 (4.3)
Junior High School	7 (16.3)	10 (43.5)
Senior High School	17 (39.5)	10 (43.5)
University	13 (30.2)	2 (8.7)
Income (Rupiah/Year), (n, %)		
<17,500,000	19 (44.2)	18 (78.3)
17,500,000 – 175,000,000	23 (53.5)	5 (21.7)
175,000,000 – 526,000,000	1 (2.3)	0 (0)
Obstetric Status		
Multiparous (n, %)	31 (72.1)	15 (65.2)
Multiple Pregnancy, (n, %)	2 (4.7)	2 (8.7)
History of pregnancy with fetal Death, (n, %)	13 (30.2)	3 (13)
Mode of Delivery, (n, %)		
Vaginal Delivery	11 (25.6)	15 (65.2)
Cesarean Section	31 (72.1)	8 (34.8)
IUFD	1 (2.3)	0 (0)
Early clinical status		
NYHA Functional Class, (n, %)		
II	3 (7.1)	5 (21.7)
III	15 (35.7)	9 (39.1)
IV	24 (57.1)	9 (39.1)
Heart rate, mean ± SD	109.6 ± 17.7	96.3 ± 17.9
Systolic BP, median (min-max)	143 (90 – 220)	120 (108 – 197)
Diastolic BP, median (min-max)	90 (60 – 160)	80 (64 – 111)
Time diagnosed, (n, %)		
Antepartum	27 (62.8)	7 (30.4)
< 1 month postpartum	12 (27.9)	8 (34.8)
1-3 months postpartum	3 (7)	8 (34.8)
3-6 months postpartum	1 (2.3)	0 (0)
Initial LVEF (%), mean ± SD	34.5 ± 7.5	33.8 ± 6.5
LVEF <30%, (n, %)	8 (20.5)	4 (19)

BP: Blood Pressure; LVEF: Left Ventricular Ejection Fraction; IUFD: Intrauterine Fetal Death; NYHA: New York Heart Association; BMI: Body Mass Index.

Table 2 illustrates differences in sFlt-1 and prolactin levels in patients with PPCM, regardless of whether they have preeclampsia. The median sFlt-1 level was found to be 128.1 pg/mL with an Interquartile Range (IQR) of 90.8–279.5 pg/mL in patients with preeclampsia. In patients without preeclampsia, the median sFlt-1 level was 94.9 pg/mL with an IQR of 82.7–110.6 pg/mL. In the group without preeclampsia, the median sFlt-1 level ranged from 59.8 to 468.8 pg/mL. The difference was significant, with a p-value of 0.046, suggesting that patients with preeclampsia tend to have higher sFlt-1 levels. However, prolactin levels showed no significant difference between the two groups, with a p-value of 0.176. However, there were significant differences in the distribution of sFlt-1 and prolactin levels between the two groups.

Table 2. Difference in sFlt-1 levels and prolactin levels in PPCM with/or without preeclampsia.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia	P Value
	n=43	n=23	
sFlt-1 Level (pg/ml)			
Median (IQR)	128.1 (90.8 – 279.5)	94.9 (82.7 – 110.6)	0.046*
Min – Max	71.9 – 6090	59.8 – 468.8	
Prolactin Level (ng/ml)			
Median (IQR)	36.52 (15.59 – 88.58)	22.11 (12.69 – 44.25)	0.176
Min – Max	3.21 – 201	0.50 – 252.6	

Description: sFlt-1 : Soluble Fms-Like Tyrosine Kinase 1; P Value using the Whitney Mann Test, *significant P<0.05

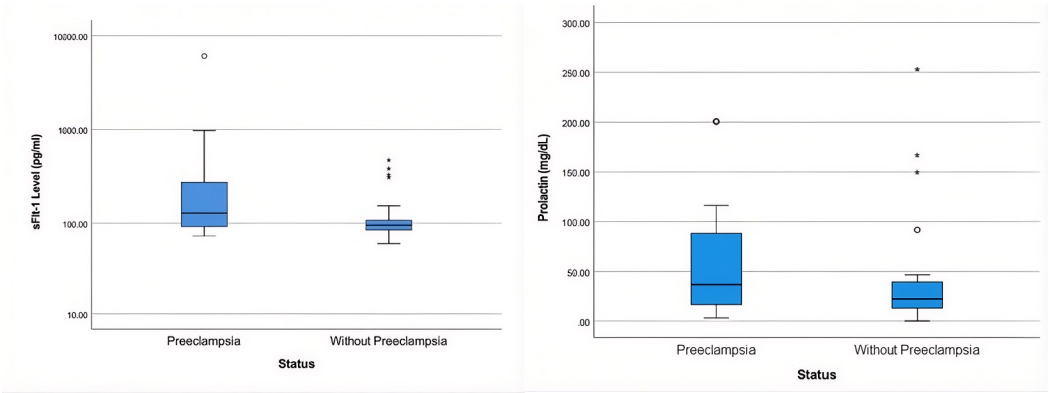

Figure 1. (A) Boxplot of differences sFlt-1 in levels in PPCM with/or without preeclampsia, (B) Boxplot of differences in prolactin levels in PPCM with/or without preeclampsia. sFlt-1 = Soluble Fms-Like Tyrosine Kinase-1

Table 3. ROC Analysis to determine high and low cut-off levels of sFlt-1 and prolactin.

Value	sFlt-1	Prolactin
AUC (95% CI)	0.650 (0.523 – 0.764)	0.602 (0.474 – 0.720)
Cut-off Value	>103.9	>34.7

sFlt-1: Soluble Fms-Like Tyrosine Kinase 1; ROC: Receiver Operating Characteristic.

Table 4: PPCM group with preeclampsia; 44.2% had high levels of sFlt-1 and prolactin (p-value of 0.002). No subjects without preeclampsia showed this combination. Conversely, low levels of sFlt-1 and prolactin were more prevalent in subjects without preeclampsia (47.8%) than in those with preeclampsia (23.2%), with a p-value of 0.002. ROC analysis for determining the cut-off values of sFlt-1 and prolactin is presented in Table 3.

Table 5 shows differences in sFlt-1 and prolactin levels among patients with PPCM by time of diagnosis. The results revealed that PPCM patients with preeclampsia had higher sFlt-1 and prolactin levels in the prepartum group than in the postpartum group. For PPCM patients without preeclampsia, however, there was no significant difference in sFlt-1 and prolactin levels by time of diagnosis.

Table 4. Distribution of sFlt-1 and prolactin levels in PPCM with/or without preeclampsia.

Variable	PPCM with Preeclampsia	PPCM without Preeclampsia	P Value
	n=43	n=23	
Combined Categories of sFlt-1 and Prolactin			0.002*
High sFlt-1 , High Prolactin	19 (44.2)	0 (0)	
High sFlt-1 , Low Prolactin	8 (18.6)	6 (26.1)	
Low sFlt-1 , High Prolactin	6 (14)	6 (26.1)	
Low sFlt-1 , Low Prolactin	10 (23.2)	11 (47.8)	

Remarks: sFlt-1: Soluble Fms-Like Tyrosine Kinase 1, P Value using Chi-Square Test, *significant P<0.05.

Table 5. Differences in sFlt-1 and prolactin levels in PPCM with and without preeclampsia based on time of diagnosis.

Variable	Timing Diagnosis			P Value
	Antepartum	<1 month postpartum	≥1 month postpartum	
PPCM with Preeclampsia	**n=27**	**n=12**	**n=4**	
sFlt-1 Level (pg/ml)				
Median (IQR)	220.1 (107.3 – 413.2)	90.6 (78.3 – 117.2)	140.8 (98 – 147.4)	0.003*
Min – Max	71.9 – 6090	73.3 – 205.1	84.0 – 149.5	
Prolactin Level (ng/ml)				
Median (IQR)	57 (21.6 – 200)	23 (10 – 33.2)	23.2 (6.8 – 63.1)	0.012*
Min – Max	8.4 – 201	3.2 – 59.3	6.8 – 70.9	
PPCM without Preeclampsia	**n=7**	**n=8**	**n=8**	
sFlt-1 Level (pg/ml)				
Median (IQR)	93.9 (79.7 – 311.1)	97 (86.9 – 103.3)	93.4 (82.2 – 268.2)	0.98
Min – Max	59.8 – 468.8	74.3 – 110.6	71.4 – 379.7	
Prolactin Level (ng/ml)				
Median (IQR)	25.1 (16.8 – 166.3)	23.8 (13.3 – 46.1)	17.5 (8.7 – 32.4)	0.537
Min – Max	11.7 – 252.6	0.5 – 149.2	6.1 – 91.7	

Remarks: P Value using the Kruskal-Wallis Test, *significant p<0.05.

Discussion

Our study showed that sFlt-1 levels were higher in the PPCM population with preeclampsia than in those without preeclampsia (Figure 1). This study is one of the first to evaluate differences in angiogenic biomarker profiles between PPCM patients with and without preeclampsia. These findings provide preliminary insight into potential variations in biomarker profiles between the two PPCM groups

Damp et al.'s "Relaxin-2 and Soluble Flt1 Levels in Peripartum Cardiomyopathy (IPAC Study)" evaluated sFlt-1 levels in patients with PPCM, but did not distinguish between those with and without preeclampsia. The study demonstrated that higher sFlt-1 levels were associated with more severe heart failure manifestations and poorer clinical outcomes.[6] These results are consistent with the possible involvement of angiogenic pathways in PPCM and suggest that sFlt-1 could be an important biomarker for this condition.

Several previous studies have also highlighted the potential heterogeneity of PPCM. For example, a review by Kryczka et al. reported that responses to bromocriptine therapy were not uniform among PPCM patients, suggesting possible variations in disease mechanisms among patients.[7] Therefore, evaluating biomarkers in PPCM subgroups with and without preeclampsia may provide additional insight into the biological characteristics of PPCM.

In the present study, higher sFlt-1 levels in the PPCM with preeclampsia group may reflect a greater contribution of angiogenic and placental factors within this subgroup. However, when interpreting these findings, it is important to consider other

clinical factors that may influence biomarker levels, such as the timing of diagnosis relative to delivery.

Prolactin (23 kDa) and its 16 kDa fragment, generated by oxidative stress, have been reported to contribute to the pathophysiology of PPCM through mechanisms involving endothelial dysfunction and myocardial apoptosis.[8] In this study, prolactin levels tended to be higher in the PPCM with preeclampsia group than in the PPCM without preeclampsia group, though the difference was not statistically significant. These results imply that the prolactin pathway may be involved in both PPCM groups.

A study by Thabat et al. demonstrated that serum prolactin levels were higher in patients with preeclampsia than in those with normal pregnancies, which may have contributed to the higher prolactin levels observed in the PPCM with preeclampsia group in the present study.[5] However, our study did not measure the 16-kDa prolactin fragment, which is thought to play the most important biological role in PPCM.

Some PPCM patients without preeclampsia in this study also showed elevated sFlt-1 and prolactin levels. These findings suggest that elevated angiogenic and prolactin-related biomarkers may also be observed in PPCM patients without preeclampsia. These results support the idea that PPCM is a multifactorial condition involving multiple biological mechanisms.[7]

This study analyzed sFlt-1 and prolactin levels according to the timing of PPCM diagnosis. The results showed that both biomarker levels tended to be higher in patients diagnosed before delivery than in those diagnosed postpartum. These results align with previous research by Damp et al., who demonstrated that sFlt-1 levels decrease after delivery.[6] Thus, the timing of diagnosis relative to delivery is a critical factor to consider when interpreting biomarker levels in PPCM.

Study Limitations

This study did not include a control group of pregnant patients with preeclampsia who did not have PPCM. Additionally, the study did not specifically examine 16-kDa prolactin, which is believed to be involved in the development of PPCM. Furthermore, analyses regarding bromocriptine use, breastfeeding, and the influence of multiple gestation and multiparity on sFlt-1 levels were not evaluated in more detail. The study had a relatively small sample size and used a retrospective observational design. Furthermore, the study was conducted at a single tertiary referral center: Dr Hasan Sadikin Hospital in Bandung. Therefore, generalization of the findings to a broader population should be approached with caution. Additionally, optimal stratification between prepartum and postpartum patients could not be achieved due to the limited sample size. The observed differences in biomarker levels should also be interpreted with caution, as differences in the timing of diagnosis relative to delivery may have contributed to the findings. Nevertheless, this study provides important preliminary data on sFlt-1 and prolactin profiles in PPCM patients with and without preeclampsia, given that studies specifically comparing these two groups remain limited. Further evaluation of the clinical and biomarker differences between these PPCM groups requires future studies with larger sample sizes and prospective designs.

Conclusion

In our study, PPCM patients with preeclampsia have higher levels of sFlt-1 than PPCM patients without preeclampsia. However, there was no statistically significant difference in prolactin levels between the two groups.

List of Abbreviations

BMI	Body Mass Index
BP	Blood Pressure
IPAC	Investigation in Pregnancy Associated Cardiomyopathy
IQR	Interquartile Range
IUFD	Intrauterine Fetal Death
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
PIGF	Placental Growth Factor
PPCM	Peripartum Cardiomyopathy
sFlt-1	Soluble Fms-Like Tyrosine Kinase-1
VEGF	Vascular Endothelial Growth Factor

Ethical Clearance

The study obtained ethical approval from the Research Ethics Committee of Padjadjaran University (No. 1383/UN6).KEP/EC/2023.

Publication Approval

The authors are approved for publication and fully understand the content of the manuscript that is submitted to the journal.

Author Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors.

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Conflict of Interest

None.

Availability of Data and Materials

The data are not publicly available due to privacy or ethical reasons but can be obtained directly from the authors upon request.

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Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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Original Article

Factors Associated with Early Acute Kidney Injury in Patients with Acute Decompensated Heart Failure: A Retrospective Observational Study in Bandung, Indonesia

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Abstract

Background: Acute Kidney Injury (AKI) frequently complicates Acute Decompensated Heart Failure (ADHF) and is associated with adverse clinical outcomes. Early recognition of patients at higher risk is clinically important, particularly during the first 48 hours of hospitalization when decongestive treatment and renal monitoring are actively adjusted.

Methods: This retrospective observational registry-based study analyzed adult patients hospitalized with ADHF at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, from January 2024 to October 2025. Of 279 screened registry records, 148 were included in the final analysis. AKI was defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours after admission. Baseline demographic, clinical, echocardiographic, treatment, and laboratory variables were evaluated using bivariate analysis and multivariable logistic regression.

Results: Among 148 included patients, AKI occurred in 67 patients (45.3%). The cohort was predominantly composed of patients with reduced Left Ventricular Ejection Fraction (LVEF), with 145 patients (98.0%) having LVEF ≤40%. Admission N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) >5000 pg/mL was associated with higher odds of early AKI in the adjusted model (Adjusted Odds Ratio [AOR] 2.04; 95% Confidence Interval [CI] 1.02-4.11; p=0.045). Hypertension and high initial furosemide dose showed nonsignificant trends, whereas other demographic and comorbidity variables did not show statistically significant associations in this cohort.

Conclusions: Elevated admission NT-proBNP was associated with early AKI among patients hospitalized with ADHF. However, these findings should be interpreted as exploratory and hypothesis-generating rather than causal or predictive. Validation in larger and more diverse cohorts is required.

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Keywords: Acute decompensated heart failure; acute kidney injury; associated factors; NT-proBNP; renal function

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Introduction

Acute Decompensated Heart Failure (ADHF) is a leading cause of hospitalization and is associated with substantial morbidity and mortality.[1-2] Renal dysfunction frequently accompanies ADHF and may manifest as Acute Kidney Injury (AKI) early during hospitalization.[3-4] Early AKI can complicate clinical management, limit decongestive treatment strategies, and contribute to worse clinical outcomes.[5-7] The reported prevalence of AKI among hospitalized patients with ADHF varies across studies, commonly ranging from approximately 20% to 40% when serum creatinine-based criteria are used, with some reviews reporting rates approaching 47% depending on case mix, baseline creatinine definition, and observation window.[6,8]

AKI in ADHF arises through multifactorial mechanisms. Reduced effective renal perfusion, neurohormonal activation, venous congestion, and treatment-related changes in intravascular volume may interact during the early phase of hospitalization.[3,9-14] Venous congestion is increasingly recognized as an important pathway in cardiorenal dysfunction because elevated venous and renal interstitial pressures can reduce glomerular filtration even when systemic arterial pressure appears acceptable.[10-11] These mechanisms support the clinical relevance of identifying baseline factors associated with early renal deterioration in ADHF.

Demographic characteristics, cardiovascular comorbidities, diuretic exposure, Left Ventricular Ejection Fraction (LVEF), and congestion-related biomarkers have all been evaluated as potential correlates of renal dysfunction in acute Heart Failure (HF).[12,15-24] Among these markers, N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) reflects myocardial wall stress and congestion severity, and is recommended in heart failure care for diagnostic and prognostic assessment.[2,23-24] However, evidence from low- and middle-income country settings remains limited, and local registry data may help clarify whether routinely available admission variables can identify patients who warrant closer early renal monitoring.

This study aimed to evaluate factors associated with early AKI among adults hospitalized with ADHF at a tertiary referral hospital in Bandung, Indonesia. The analysis focused on AKI occurring within the first 48 hours after admission and was intended to support practical early risk awareness rather than to establish causal relationships or to provide definitive predictions.

Methods

Study Design, Setting, and Ethical Considerations

This retrospective observational study used registry data on adult patients hospitalized with ADHF at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. The registry period included admissions from January 2024 to October 2025. Baseline admission variables were evaluated in relation to AKI occurring within the first 48 hours of hospitalization. Because this analysis was based on existing registry records and did not involve prospective follow-up beyond the early hospitalization window, the findings were interpreted as associations rather than causal or predictive effects. The study received ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (DP.04.03/D. XIV.6.5/591/2025).

Participants and Eligibility Criteria

Records were eligible for inclusion if patients were aged 18 years or older and had a documented diagnosis of ADHF during the early phase of hospitalization. Records were excluded if key variables required for outcome or exposure assessment were incomplete, if patients had end-stage kidney disease receiving chronic maintenance dialysis, including hemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD), or if they had a history of kidney transplantation.

Study Variables

Baseline variables evaluated in this study included age category, sex, history of hypertension, coronary artery disease, prior heart failure, diabetes mellitus, initial furosemide therapy dose, LVEF category, and admission NT-proBNP category. These variables were selected because they were clinically plausible and available in the ADHF registry. The term "associated factors" was used throughout the manuscript because the retrospective observational design does not support causal inference.

Baseline Creatinine Definition and Imputation

Baseline serum creatinine was defined as the first available creatinine value recorded in the registry at hospital admission. When the baseline creatinine value was missing, serum creatinine was imputed using the New Linear Equation (New-LE), an age- and sex-based formula: baseline serum creatinine (μmol/L) = 55.2 + (0.525 × age in years) - 15.0 for female patients, whereas no subtraction was applied for male patients. Estimated values in μmol/L were converted to mg/dL by dividing by 88.4. The final

baseline value used for analysis was the measured admission creatinine when available or the New-LE-estimated creatinine when the measured value was missing. This approach was prespecified, but it may introduce classification uncertainty and was therefore considered in the interpretation of findings.

Outcome Definition

The primary outcome was early AKI, defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours after admission, consistent with the creatinine component of the Kidney Disease: Improving Global Outcomes (KDIGO) AKI definition.[37] AKI ascertainment was based on the final baseline serum creatinine value, and the creatinine level was measured approximately 48 hours after admission. Urine output criteria were not used because urine output data were not consistently available in the registry.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27. Categorical variables were summarized as counts and proportions. Continuous variables were summarized as the mean with standard deviation or as the median with minimum and maximum values, as appropriate. Bivariate associations were assessed using the chi-square test or Fisher's exact test. Variables with a bivariate p-value <0.25 were entered into a multivariable logistic regression model to estimate Adjusted Odds Ratios (aORs) with 95% Confidence Intervals (CIs). Statistical significance was defined as a two-sided p-value <0.05. Because several exposure categories contained small numbers of patients, all estimates were interpreted cautiously, with attention to confidence interval width and proximity to the null value.

Results

This study used secondary data from the ADHF registry at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. A total of 279 registry records from January 2024 to October 2025 were screened. Of these, 122 records were excluded because of incomplete registry data, and 9 records were excluded because of a history of end-stage chronic kidney disease. The final analytic sample comprised 148 records that met the eligibility criteria. The patient selection process is summarized in Figure 1.

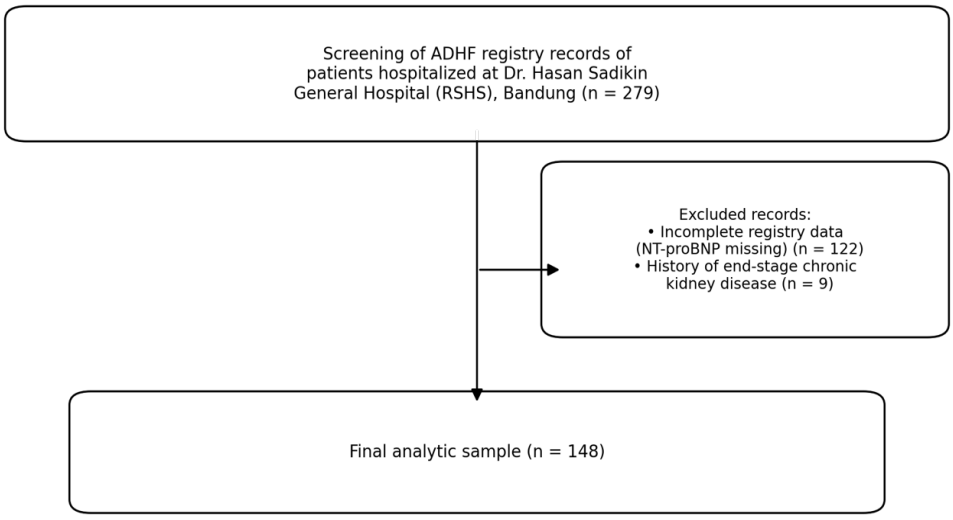

Figure 1. Flow of registry record selection for the study population.

Table 1 shows the baseline characteristics of the included patients. The mean age was 54 ± 13 years. Patients younger than 60 years constituted the majority (98 patients, 66.2%), whereas 50 patients (33.8%) were aged 60 years or older. Male patients predominated (90 patients, 60.8%). Hypertension was present in 72 patients (48.6%), diabetes mellitus in 47 patients (31.8%), coronary artery disease in 50 patients (33.8%), and prior heart failure in 109 patients (73.6%). All patients received furosemide at the beginning of hospitalization. A low initial dose was administered to 136 patients (91.9%), whereas a high initial dose was administered to 12 patients (8.1%). The median LVEF was 24% (range, 12-57%). Most patients had LVEF ≤40% (145 patients, 98.0%), whereas only 3 patients (2.0%) had LVEF >40%. The median NT-proBNP level was 6539.5 pg/mL (range, 16-25000 pg/mL), and 91 patients (61.4%) had NT-proBNP >5000 pg/mL. Overall, this cohort was dominated by patients with Heart

Failure with reduced Ejection Fraction (HFrEF) and substantial biomarker evidence of congestion.

Table 2 shows renal function parameters during the first 48 hours of hospitalization. The median admission serum creatinine was 0.92 mg/dL (range, 0.44-2.95 mg/dL). After 48 hours, the median serum creatinine increased to 1.19 mg/dL (range, 0.56-3.74 mg/dL). The median change in creatinine was 0.25 mg/dL, ranging from a decrease of -0.44 mg/dL to a maximum increase of 2.00 mg/dL. Using the criterion of a serum creatinine increase of at least 0.3 mg/dL, 67 patients (45.3%) developed early AKI, whereas 81 patients (54.7%) did not.

Table 1. Characteristics of study participants with acute decompensated heart failure.

Variable	n = 148
Age (years), mean ± SD	54 ± 13
Age category, n (%)	
60 years or older	50 (33.8)
Younger than 60 years	98 (66.2)
Sex, n (%)	
Female	58 (39.2)
Male	90 (60.8)
History of hypertension, n (%)	
Yes	72 (48.6)
No	76 (51.4)
History of coronary artery disease, n (%)	
Yes	50 (33.8)
No	98 (66.2)
Prior history of heart failure, n (%)	
Yes	109 (73.6)
No	39 (26.4)
History of diabetes mellitus, n (%)	
Yes	47 (31.8)
No	101 (68.2)
Initial furosemide therapy, n (%)	
High dose	12 (8.1)
Low dose	136 (91.9)
LVEF (%), median (min–max)	24 (12–57)
LVEF category, n (%)	
40% or lower	145 (98.0)
Greater than 40%	3 (2.0)
NT-proBNP (pg/mL), median (min–max)	6539.5 (16–25000)
NT-proBNP category, n (%)	
Greater than 5000 pg/mL	91 (61.4)
5000 pg/mL or lower	57 (38.6)

Abbreviations: SD = standard deviation; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 3 shows the bivariate analyses of factors associated with early AKI. No statistically significant association was observed between AKI and age category (p=0.899; Odds Ratio [OR] 0.96; 95% CI 0.48-1.89) or sex (p=0.801; OR 1.09; 95% CI 0.56-2.11). Hypertension showed a nonsignificant trend toward higher odds of AKI, with AKI occurring in 52.8% of patients with hypertension and 38.2% of those without hypertension (p=0.074; OR 1.81; 95% CI 0.94-3.49). Histories of coronary artery disease, prior heart failure, and diabetes mellitus did not show statistically significant associations. High initial furosemide dose showed a nonsignificant trend toward lower odds of AKI (16.7% in the high-dose

group versus 47.8% in the low-dose group; p=0.066; OR 0.22; 95% CI 0.05-1.03). LVEF category did not show a statistically significant association, although interpretation was limited by the very small number of patients with LVEF >40%.

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Table 2. Serum creatinine distribution and acute kidney injury incidence in patients with acute decompensated heart failure.

Variable	n = 148
Admission serum creatinine (mg/dL), median (min–max)	0.92 (0.44–2.95)
Serum creatinine at 48 hours (mg/dL), median (min–max)	1.19 (0.56–3.74)
Δ creatinine (mg/dL), median (min–max)	0.25 (−0.44–2.00)
Acute kidney injury (AKI), n (%)	
Yes (serum creatinine increase ≥ 0.3 mg/dL)	67 (45.3)
No	81 (54.7)

Table 3. Bivariate analysis of factors associated with acute kidney injury in patients with acute decompensated heart failure.

Variable	Total (n = 148)	AKI: Yes (n = 67)	AKI: No (n = 81)	p value	OR (95% CI)
Age category, n (%)					
60 years or older	50	23 (46.0)	27 (54.0)	0.899a	0.96 (0.48–1.89)
Younger than 60 years	98	44 (44.9)	54 (55.1)		1.00 (ref)
Sex, n (%)					
Female	58	27 (46.6)	31 (53.4)	0.801a	1.09 (0.56–2.11)
Male	90	40 (44.4)	50 (55.6)		1.00 (ref)
History of hypertension, n (%)					
Yes	72	38 (52.8)	34 (47.2)	0.074a	1.81 (0.94–3.49)
No	76	29 (38.2)	47 (61.8)		1.00 (ref)
History of coronary artery disease, n (%)					
Yes	50	22 (44.0)	28 (56.0)	0.825a	0.93 (0.47–1.84)
No	98	45 (45.9)	53 (54.1)		1.00 (ref)
Prior history of heart failure, n (%)					
Yes	109	47 (43.1)	62 (56.9)	0.379a	0.72 (0.35–1.50)
No	39	20 (51.3)	19 (48.7)		1.00 (ref)
History of diabetes mellitus, n (%)					
Yes	47	22 (46.8)	25 (53.2)	0.798a	1.10 (0.55–2.19)
No	101	45 (44.6)	56 (55.4)		1.00 (ref)
Initial furosemide therapy, n (%)					
High dose	12	2 (16.7)	10 (83.3)	0.066a	0.22 (0.05–1.03)
Low dose	136	65 (47.8)	71 (52.2)		1.00 (ref)

LVEF category, n (%)					
40% or lower	145	65 (44.8)	80 (55.2)	0.452b	0.41 (0.04–4.58)
Greater than 40%	3	2 (66.7)	1 (33.3)		1.00 (ref)
NT-proBNP category, n (%)					
Greater than 5000 pg/mL	91	47 (51.6)	44 (48.4)	0.049a*	1.98 (1.00–3.91)
5000 pg/mL or lower	57	20 (35.1)	37 (64.9)		1.00 (ref)

Notes: p values were calculated using a Chi-square test or b Fisher's exact test; *statistically significant at $p < 0.05$.

Table 4. Multivariable analysis of factors associated with acute kidney injury.

Variable	aOR (95% CI)	p value
Hypertension	1.79 (0.91–3.51)	0.092
High-dose initial furosemide therapy	0.24 (0.05–1.15)	0.075
High NT-proBNP (greater than 5000 pg/mL)	2.04 (1.02–4.11)	0.045*

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; *statistically significant at $p < 0.05$. Variables entered into the multivariable model were those with bivariate p values < 0.25.

Table 4 shows the multivariable logistic regression analysis. After adjustment for variables with bivariate p-values <0.25, admission NT-proBNP >5000 pg/mL remained associated with higher odds of early AKI (aOR 2.04; 95% CI 1.02-4.11; p=0.045). Hypertension showed a nonsignificant trend toward higher odds of AKI (aOR 1.79; 95% CI 0.91-3.51; p=0.092), whereas high initial furosemide dose showed a nonsignificant trend toward lower odds (aOR 0.24; 95% CI 0.05-1.15; p=0.075). These adjusted estimates should be interpreted as exploratory due of the limited sample size, small numbers in some exposure categories, and CIs close to the null.

Discussion

This retrospective registry-based study found that early AKI occurred in 45.3% of adults hospitalized with ADHF at a tertiary referral hospital in Bandung, Indonesia. The proportion was within the upper range of prior estimates in acute heart failure populations and may reflect the severity of systolic dysfunction and congestion in this cohort.[3,5-6,8] The main finding was that admission NT-proBNP >5000 pg/mL was associated with approximately twofold higher adjusted odds of early AKI. However, the CI was close to unity, and the finding should be interpreted as an exploratory signal rather than as evidence of an independent predictive effect.

The association between elevated NT-proBNP and early AKI is biologically plausible. NT-proBNP reflects myocardial wall stress and congestion severity, and contemporary heart failure literature recognizes venous congestion as a key contributor to kidney dysfunction.[10-11,23-24] Increased central venous pressure, renal venous pressure, and renal interstitial pressure can reduce the glomerular filtration gradient and impair renal function, even when arterial pressure appears adequate.[10,32] These mechanisms are consistent with cardiorenal syndrome frameworks that position congestion as both a marker of disease severity and a contributor to renal vulnerability.[9,33]

These findings also align with current guideline-oriented care, while adding a local exploratory observation. The 2022 AHA/ACC/HFSA Heart Failure Guideline supports measuring natriuretic peptides for diagnostic and prognostic assessment in HF, including in hospitalized patients.[2] The 2024 American Heart Association scientific statement on kidney dysfunction in HF emphasizes that renal function must be interpreted within the broader clinical trajectory of HF and congestion.[4] Meanwhile, KDIGO criteria define AKI using serum creatinine changes and urine output, and the present study used only the creatinine component because registry urine output was incomplete.[37] In this context, NT-proBNP should not be interpreted as a stand-alone predictor of AKI, but it may help clinicians identify patients who require closer creatinine monitoring, careful decongestion assessment, and more cautious interpretation of early renal function changes.

The local setting is relevant because ADHF care in low- and middle-income countries often depends on routinely available registry variables rather than advanced hemodynamic monitoring or

novel renal biomarkers. A simple admission marker such as NT-proBNP may therefore have practical value as a signal for early monitoring. Nevertheless, the present findings should not be used to change therapy on their own. Instead, they support the need for larger local and multicenter studies that integrate biomarkers, fluid balance, diuretic response, blood pressure trajectories, and objective assessment of congestion.

No statistically significant associations were observed for age category, sex, coronary artery disease, prior HF, or diabetes mellitus. These results should not be interpreted as a definitive absence of association. The study was not powered to detect small or moderate effects across multiple variables, and several exposure groups were small. Similarly, hypertension and high initial furosemide dose showed nonsignificant trends, but these estimates may be unstable. The trend toward higher-dose furosemide may reflect treatment selection, differences in the congestion phenotype, or unmeasured clinical factors rather than a protective effect.[12-14] Future analyses should include diuretic response, urine output, fluid balance, and congestion markers to clarify this relationship.

The predominance of HFrEF in this cohort is an important consideration. Almost all included patients had LVEF ≤40%, and only 3 patients had LVEF >40%. Therefore, the findings primarily apply to patients with reduced ejection fraction and should not be generalized to patients with Heart Failure with mildly reduced Ejection Fraction (HFmrEF) or Heart Failure with preserved Ejection Fraction (HFpEF). Prior studies suggest that the relationship between LVEF phenotype and worsening renal function may differ across acute HF subgroups, and broader representation of HFmrEF and HFpEF is needed before conclusions can be extended to those populations.[35-36]

Strengths of this study include the use of real-world registry data from a tertiary referral hospital and the focus on a clinically meaningful early hospitalization window. The study also explicitly described its approach to baseline creatinine ascertainment, which is important because this can substantially influence AKI classification and comparability across cohorts.[28-31]

This study has several limitations. First, its retrospective observational design limits causal inference and creates susceptibility to residual confounding. Second, 131 of 279 screened records were excluded, mainly because of incomplete registry data. This may have introduced selection bias and may limit representativeness. Third, the sample size was modest, and some exposure categories were very small, especially high initial furosemide dose and LVEF >40%, which reduced statistical power and precision of estimates. Fourth, the association between NT-proBNP and AKI was borderline, with the CI close to the null value. Fifth, AKI was defined using serum creatinine within 48 hours and did not include urine output criteria. Sixth, admission creatinine and New-LE imputation were used when measured baseline values were unavailable, which may have led to misclassification, particularly if renal dysfunction had already begun before admission. Finally, the single-center setting and predominance of HFrEF limit generalizability.

Future studies should prospectively evaluate renal trajectories beyond 48 hours and incorporate urine output, fluid balance, congestion measures, hemodynamic variables, and diuretic response. External validation across hospitals and HF phenotypes will be important to determine whether admission NT-proBNP can be incorporated into locally applicable tools for early renal monitoring in ADHF.

Conclusion

Early AKI was common among adults hospitalized with ADHF at Dr. Hasan Sadikin General Hospital, Bandung, occurring in 45.3% of included patients within 48 hours of admission. Admission NT-proBNP >5000 pg/mL was associated with higher adjusted odds of early AKI.

These findings suggest that elevated NT-proBNP may serve as a practical signal for closer early renal monitoring in ADHF, particularly in settings where advanced congestion or renal biomarkers are not routinely available. However, the study should be viewed as exploratory and hypothesis-generating. Therefore, larger prospective, multicenter studies are needed to validate this association and determine whether NT-proBNP adds value to clinical risk assessment for early AKI in ADHF.

List of Abbreviations

ADHF	Acute Decompensated Heart Failure
AKI	Acute Kidney Injury
aOR	Adjusted Odds Ratio
CAPD	Continuous Ambulatory Peritoneal Dialysis
CI	Confidence Interval
HF	Heart Failure

HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
KDIGO	Kidney Disease: Improving Global Outcomes
LVEF	Left Ventricular Ejection Fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	Odds Ratio

Ethical Clearance

This study received ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran (DP.04.03/D. XIV.6.5/591/2025).

Publication Approval

All authors are consent to the publication of this manuscript.

Author Contributions

HSP and FYR conceptualized the study; HSP, FYR, RA, IW, JWM, and LS contributed to methodology, analysis, interpretation, manuscript drafting, and critical revision.

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Conflict of Interest

The authors declare no conflicts of interest.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request and with permission from Dr. Hasan Sadikin General Hospital.

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Original Article

Right Heart Catheterization Hemodynamic Parameters and Cardiovascular Adverse Events in Advanced Heart Failure: A Retrospective Cohort Study

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Abstract

Background: Right Heart Catheterization (RHC) is an important tool in advanced heart failure because it provides invasive assessment of hemodynamics, congestion, pulmonary hypertension, and right ventricular function, and helps determine candidacy for advanced therapies. However, the prognostic value of RHC-derived hemodynamic parameters in real-world advanced heart failure remains unclear. This study aimed to describe the clinical, echocardiographic, and invasive hemodynamic characteristics of patients with advanced heart failure undergoing RHC and to explore their association with Cardiovascular Adverse Events (CVAE).

Methods: This retrospective cohort study was conducted at two tertiary referral centers in Indonesia. Consecutive adult patients with advanced heart failure who underwent RHC were included. The primary outcome was CVAE, defined as a composite of cardiovascular death or rehospitalization due to acute heart failure, arrhythmia, or cardiogenic shock during a median follow-up of 6 (IQR 3-12) months after the index RHC. Baseline clinical, echocardiographic, and invasive hemodynamic data were collected from medical records and catheterization reports. No formal sample size calculation was performed. Patients with and without CVAE were compared, and bivariate logistic regression was used to explore associations between hemodynamic parameters and CVAE.

Results: A total of 33 patients were included, and 22 (68.6%) developed CVAE. Mean age was 48.0 ± 11.3 years, and 29 patients (87.9%) were male. Most patients were INTERMACS profile 4, and 27 (81.8%) had combined post- and pre-capillary pulmonary hypertension. Compared with 11 patients without CVAE, the 22 patients with CVAE had lower cardiac output (3.23 ± 0.8 vs 3.99 ± 1.1 L/min; p=0.027), lower cardiac index (1.85 ± 0.4 vs 2.34 ± 0.7 L/min/m^2; p=0.019), and lower pulmonary artery pulsatility index (0.56 [0.14-1.31] vs 1.35 [0.53-4.38]; p=0.044). Other hemodynamic parameters were not significantly different. In bivariate logistic regression, higher cardiac output, cardiac index, and pulmonary artery pulsatility index were associated with lower odds of CVAE.

Conclusions: In this two-center retrospective cohort of patients with advanced heart failure undergoing RHC, lower cardiac output, lower cardiac index, and lower pulmonary artery pulsatility index were associated with CVAE, whereas conventional pressure-based and pulmonary vascular parameters were not. These findings suggest that impaired forward flow and reduced right ventricular-pulmonary arterial pulsatile reserve may be important for risk stratification in advanced heart failure.

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Keywords: Advanced heart failure, Right heart catheterization, Hemodynamics, Cardiovascular adverse events

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Introduction

Advanced heart failure represents the most severe stage of the heart failure spectrum and is characterized by persistent symptoms, recurrent decompensation, poor exercise tolerance, repeated hospitalization, and high mortality despite guideline-directed therapy. In this population, accurate hemodynamic profiling is clinically important because bedside examination and noninvasive testing may not fully capture the severity or mechanism of circulatory impairment. Current heart failure guidance, therefore, recognizes Right Heart Catheterization (RHC) as a valuable tool in selected patients with advanced disease, particularly when there is persistent congestion, suspected low-output state, pulmonary hypertension, right ventricular dysfunction, cardiogenic shock, or the need to evaluate candidacy for advanced therapies such as durable mechanical circulatory support or heart transplantation.[1-3]

Beyond diagnosis, invasive hemodynamic assessment may provide prognostic information. Conventional RHC variables such as Right Atrial Pressure (RAP), Pulmonary Capillary Wedge Pressure (PCWP), Pulmonary Artery Pressure (PAP), Cardiac Output (CO), Cardiac Index (CI), and Pulmonary Vascular Resistance (PVR) reflect different but interrelated domains of advanced heart failure, including congestion, forward flow, pulmonary vascular load, and right ventricular–pulmonary arterial coupling. More recently, interest has expanded to integrative parameters such as Pulmonary Artery Pulsatility index (PAPi), Pulmonary Artery Compliance (PAC), and the RAP/PCWP ratio, which may better reflect right-sided reserve and the hemodynamic consequences of biventricular dysfunction. Contemporary reviews emphasize that these invasive measurements are not merely descriptive, but may help identify patients at higher risk of adverse outcomes and refine clinical decision-making in advanced heart failure and shock states.[3-5]

However, the prognostic relevance of individual RHC parameters remains incompletely defined, particularly in real-world populations with mixed etiologies of advanced heart failure. Most available evidence on advanced heart failure hemodynamics has been generated from high-volume centers, transplant-oriented cohorts, or healthcare systems with more established access to durable mechanical circulatory support and heart transplantation. In contrast, regional heart failure registries from Asia and Southeast Asia have described important differences in patient age, comorbidity profiles, treatment patterns, and outcomes, but invasive hemodynamic data remain limited. This gap is relevant because access to RHC, advanced heart failure programs, and mechanical circulatory support varies substantially across healthcare systems, potentially influencing case selection and the hemodynamic phenotype of patients undergoing invasive assessment.[1-4] In Indonesia, where RHC is still performed in a limited number of centers, local data describing the hemodynamic characteristics and clinical implications of invasive assessment in advanced heart failure are scarce. Accordingly, this study aimed to describe the clinical, echocardiographic, and invasive hemodynamic profiles of patients with advanced heart failure undergoing RHC in our center and to explore the association between RHC-derived parameters and Cardiovascular Adverse Events (CVAE), defined as cardiovascular death or rehospitalization due to acute heart failure, arrhythmia, or cardiogenic shock.

Methods

Study Design and Setting

This was a retrospective observational cohort study conducted at two tertiary referral centers in Indonesia: National Cardiovascular Center Harapan Kita, Jakarta, and Dr. Hasan Sadikin General Hospital, Bandung. Consecutive adult patients with advanced heart failure who underwent clinically indicated RHC between April 2023 and January 2026 were reviewed. We reviewed consecutive patients with advanced heart failure who underwent RHC as part of their clinical evaluation. The study was designed to describe the clinical, echocardiographic, and invasive hemodynamic characteristics of this population and to explore the association between RHC-derived parameters and subsequent CVAE. Because the study reflected real-world clinical practice in two tertiary referral centers where RHC is performed selectively in patients with advanced heart failure, no study-specific intervention was applied. All diagnostic and therapeutic decisions were made by the treating physicians according to routine institutional practice.

Study Population

The study population consisted of adult patients with advanced heart failure who underwent RHC during the study period. The process of patient screening, exclusion, and final cohort selection is summarized in Figure 1. Patients were eligible for inclusion if they had complete baseline clinical

data, echocardiographic assessment, and invasive hemodynamic measurements obtained during the index RHC procedure. Advanced heart failure was defined according to established clinical criteria, including persistent severe symptoms despite guideline-directed medical therapy, recurrent heart failure decompensation, evidence of low-output physiology or refractory congestion, need for advanced heart failure evaluation, or consideration for advanced therapies such as heart transplantation or durable mechanical circulatory support. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles were used to further characterize the severity of advanced heart failure when available. INTERMACS profile 3 was defined as stable but inotrope dependent, whereas INTERMACS profile 4 was defined as resting symptoms despite optimized oral therapy.

Exclusion criteria were incomplete RHC data, unavailable key outcome data during follow-up, severe primary valvular heart disease as the main etiology of heart failure, and catheterization performed for indications not primarily related to advanced heart failure assessment. For patients who underwent more than one RHC, only data from the index catheterization were included in the analysis.

Data Collection

Clinical data were collected retrospectively, and baseline variables included demographic characteristics, cardiovascular risk factors, heart failure etiology, New York Heart Association (NYHA) functional class, cardiac rhythm, and echocardiographic parameters. Echocardiographic variables included Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Diameter (LVEDD), Tricuspid Regurgitation Maximum velocity (TRVmax), and Left Atrial Volume Index (LAVI), where available.

Invasive hemodynamic data obtained from the index RHC included RAP, mean PAP, PCWP, CO, CI, PVR, PAC, Right Ventricular Stroke Work Index (RVSWI), PAPi, and RAP/PCWP ratio. CO was measured using thermodilution, according to the institutional catheterization protocol. Hemodynamic variables were recorded from the catheterization report and calculated according to standard definitions used in routine clinical practice. CI was calculated as cardiac output divided by body surface area. Pulmonary vascular resistance was calculated as PVR = (mean PAP − PCWP) / CO. PAPi was calculated as PAPi = (systolic PAP − diastolic PAP) / RAP. PAC was calculated as PAC = stroke volume / pulmonary artery pulse pressure. The RAP/PCWP ratio was calculated by dividing right atrial pressure by PCWP. RVSWI was calculated as RVSWI = (mean PAP − RAP) × stroke volume index × 0.0136. Detailed operational definitions of the hemodynamic parameters are provided in Supplementary Table S1.

Pulmonary hypertension subtype was categorized based on invasive hemodynamic measurements into isolated post-capillary pulmonary hypertension or combined post- and pre-capillary pulmonary hypertension. Right ventricular dysfunction was also evaluated using predefined study criteria based on the available hemodynamic parameters.

In addition, data on baseline heart failure treatment were collected, including guideline-directed medical therapy, selected adjunctive therapies, device therapy, and advanced heart failure status. Guideline-directed medical/device therapy included Angiotensin-Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor–Neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid receptor antagonist, sodium-glucose cotransporter-2 inhibitor, loop diuretic, tolvaptan, ivabradine, levosimendan, and Implantable Cardioverter-Defibrillator (ICD)/Cardiac Resynchronization Therapy (CRT), where applicable. Advanced heart failure status was categorized according to the treating team's clinical assessment as a candidate for heart transplantation, a candidate for Left Ventricular Assist Device (LVAD), or end-stage heart failure/not suitable for advanced therapy.

Study Outcome

The primary outcome of this study was CVAE, defined as a composite of cardiovascular death or rehospitalization attributable to acute heart failure, arrhythmia, or cardiogenic shock. Outcome status was assessed using follow-up records after the index right heart catheterization, and patients were subsequently categorized as having CVAE or not for comparative analysis. Follow-up duration was calculated from the date of index RHC to the date of first CVAE, cardiovascular death, last clinical follow-up, or the end of the study observation period, whichever occurred first. Median follow-up duration was 6 (Interquartile Range [IQR] 3-12) months.

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (IQR), as appropriate, and categorical variables as frequencies and percentages. Differences between patients with CVAE and patients without CVAE were assessed using the independent-samples t-test or Mann–Whitney U

test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Associations between hemodynamic parameters and CVAE were explored using bivariate logistic regression and are presented as Odds Ratios (ORs) with 95% Confidence Intervals (CIs). No formal sample size calculation was performed because this was a retrospective exploratory study based on all eligible patients who underwent clinically indicated RHC during the study period. Given the small sample size and limited number of events, no multivariable model was constructed, and all regression findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory. In view of the small sample size and limited number of events, these regression analyses were considered exploratory. A two-sided p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 29.0.2.0 (IBM Corp., Armonk, NY, USA).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of National Cardiovascular Center Harapan Kita, Jakarta (protocol no LB.02.01A/II/028/KEP028/2023) and Dr. Hasan Sadikin General Hospital, Bandung (protocol no. KP.04.04/D.XIV.3.4.23/271/2025). Because this study involved a retrospective analysis of anonymized registry data, the ethics committee waived the requirement for informed consent.

Results

A total of 113 adult patients who underwent RHC at the two participating centers were screened; of these, 33 met the study criteria and were included in the final analysis, as detailed in Figure 1. At a median follow-up of 6 months (IQR 3-12) after the index RHC, 22 patients (68.6%) experienced CVAE, while 11 (31.4%) did not. The mean age of the overall cohort was 48.0 ± 11.3 years, and most patients were male (87.9%). Most participants were in NYHA functional class III (75.8%), followed by class IV (24.2%). Ischemic cardiomyopathy was the most common etiology (48.5%), followed by non-ischemic cardiomyopathy (30.3%). Baseline clinical characteristics, cardiovascular risk factors, and heart failure etiology were generally comparable between patients with CVAE and patients without CVAE (Table 1). Echocardiographic parameters, including LVEF and LVEDD, also did not differ significantly between the two groups. Likewise, LAVI was not significantly different between patients with CVAE and patients without CVAE (p = 0.264) (Table 1).

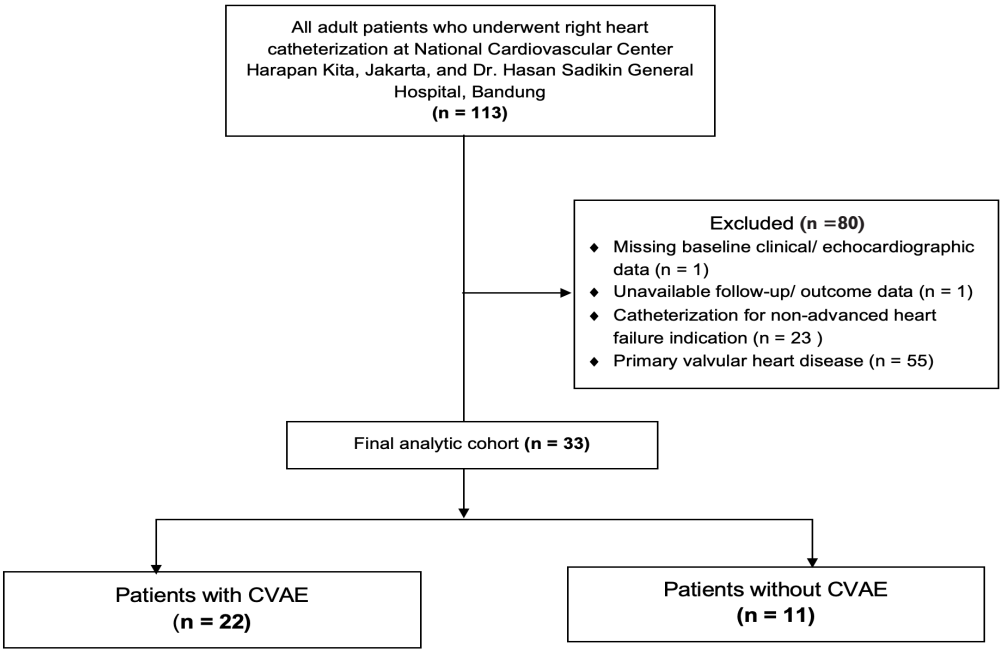

Figure 1. Flow diagram showing patient exclusion and inclusion in the final analytic cohort of patients with advanced heart failure who underwent right heart catheterization at National Cardiovascular Center, Harapan Kita, Jakarta, and Dr. Hasan Sadikin General Hospital, Bandung.

Table 1. Baseline characteristics of patients with advanced heart failure undergoing right heart catheterization.

Variable	All patients (n=33)	Patients with CVAE (n=22)	Patients without CVAE (n=11)	P-value
Age, years	48.00 ± 11.3	47.82 ± 10.9	48.36 ± 10.4	0.894
Male sex, n (%)	29 (87.9)	20 (90.9)	9 (81.8)	0.586
Body mass index category, n (%)				0.493
Normal	18 (54.5)	11 (50.0)	7 (63.6)	
Underweight	6 (18.2)	5 (22.7)	1 (9.1)	
Overweight	5 (15.2)	4 (18.2)	1 (9.1)	
Obesity grade 1	1 (3.0)	1 (4.5)	0 (0.0)	
Obesity grade 2	3 (9.1)	1 (4.5)	2 (18.2)	
NYHA functional class, n (%)				0.566
III	25 (75.8)	16 (72.7)	9 (81.8)	
IV	8 (24.2)	6 (27.3)	2 (18.2)	
INTERMACS profile, n (%)				0.132
Profile 3 (stable but inotrope dependent)	13 (39.4)	11 (50.0)	2 (18.2)	
Profile 4 (resting symptoms)	20 (60.6)	11 (50.0)	9 (81.8)	
Risk factors, n (%)				
Hypertension	11 (33.3)	8 (36.4)	3 (27.3)	0.709
Current/former smoker	16 (48.5)	9 (40.9)	7 (63.6)	0.218
Dyslipidemia	6 (18.2)	4 (18.2)	2 (18.2)	1.000
Diabetes mellitus	10 (30.3)	8 (36.4)	2 (18.2)	0.430
eGFR, mL/min/1.73 m²	61.20 ± 20.2	60.69 ± 19.1	62.21 ± 23.2	0.843
ECG rhythm, n (%)				0.071
Sinus rhythm	25 (75.8)	14 (63.6)	11 (100.0)	
Atrial fibrillation	7 (21.2)	7 (31.8)	0 (0.0)	
Atrial flutter	1 (3.0)	1 (4.5)	0 (0.0)	
Heart failure etiology, n (%)				
Ischemic cardiomyopathy	16 (48.5)	12 (54.5)	4 (36.4)	0.325
Non-ischemic cardiomyopathy	11 (33.3)	6 (27.3)	5 (45.5)	0.437
Valvular heart disease	4 (12.1)	3 (13.6)	1 (9.1)	1.000
Dual cardiomyopathy	2 (6.1)	1 (4.5)	1 (9.1)	1.000
Echocardiography				
LVEF, %	26.89 ± 12.4	25.84 ± 9.5	29.00 ± 17.2	0.500
LVEDD, mm	63.89 ± 11.7	66.14 ± 11.6	59.39 ± 11.0	0.260
Moderate/severe mitral regurgitation, n (%)	14 (42.4)	9 (40.9)	5 (45.5)	1.000
Moderate/severe mitral stenosis, n (%)	1 (3.0)	1 (4.5)	0 (0.0)	1.000
Moderate/severe tricuspid regurgitation, n (%)	18 (54.5)	11 (50.0)	7 (63.6)	0.458
Moderate aortic regurgitation, n (%)	1 (3.0)	0 (0.0)	1 (9.1)	0.333
Moderate aortic stenosis, n (%)	1 (3.0)	0 (0.0)	1 (9.1)	0.333
TAPSE, mm	14.42 ± 3.5	14.94 ± 3.5	13.61 ± 3.2	0.681
TR Vmax, m/s	2.53 ± 0.9	2.31 ± 0.7	2.88 ± 0.9	0.080

LAVI, mL/m²	63.00 (47.37–84.00)	69.44 (47.93–93.00)	53.20 (45.00–71.00)	0.264
Guideline-directed medical/device therapy, n (%)				
ACEi/ARNI	27 (81.8)	19 (86.4)	8 (72.7)	0.375
Beta-blocker	9 (27.3)	5 (22.7)	4 (36.4)	0.438
Mineralocorticoid receptor antagonist	28 (84.8)	20 (90.9)	8 (72.7)	0.304
SGLT2 inhibitor	5 (15.2)	2 (9.1)	3 (27.3)	0.304
Loop diuretic	29 (87.9)	19 (86.4)	10 (90.9)	1.000
Tolvaptan	4 (12.1)	2 (9.1)	2 (18.2)	0.586
Ivabradine	8 (24.2)	3 (13.6)	5 (45.5)	0.082
Levosimendan	11 (33.3)	8 (36.4)	3 (27.3)	0.709
ICD/CRT	3 (9.1)	1 (4.5)	2 (18.2)	0.252
Advanced HF status, n (%)				0.090
Candidate for heart transplant	10 (30.3)	4 (18.2)	6 (54.5)	
Candidate for LVAD	16 (48.5)	12 (54.5)	4 (36.4)	
End-stage HF/not suitable for advanced therapy	7 (21.2)	6 (27.3)	1 (9.1)	

Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronization therapy; CVAE, cardiovascular adverse event; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LAVI, left atrial volume index; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter-2; TAPSE, tricuspid annular plane systolic excursion; TR Vmax, tricuspid regurgitation maximum velocity.

Baseline treatment profiles also reflected an advanced heart failure cohort. Most patients were receiving renin–angiotensin system inhibition (ACEi/ARNI, 81.8%), mineralocorticoid receptor antagonists (84.8%), and loop diuretics (87.9%), whereas beta-blocker use was less frequent (27.3%). Device therapy with ICD/CRT was present in 9.1% of patients. Regarding advanced heart failure status, 30.3% were considered candidates for heart transplantation, 48.5% candidates for LVAD, and 21.2% were classified as end-stage heart failure/not suitable for advanced therapy. Most patients were classified as INTERMACS profile 4 (resting symptoms), while the remainder were in INTERMACS profile 3 (stable but inotrope-dependent), further supporting the conclusion that this was a clinically advanced and high-risk heart failure cohort.

The hemodynamic profile of the overall cohort showed a median RAP of 11.00 mmHg (IQR 6.50–18.00), mean PAP of 34.90 ± 9.1 mmHg, mean PCWP of 22.79 ± 6.2 mmHg, mean CO of 3.48 ± 0.9 L/min, and mean CI of 2.01 ± 0.6 L/min/m², which were consistent with advanced heart failure hemodynamic profiles. Most patients had combined post- and pre-capillary pulmonary hypertension (81.8%), while the remaining 18.2% had isolated post-capillary pulmonary hypertension; no patient had isolated pre-capillary pulmonary hypertension. RV dysfunction was present in 30.3% of the cohort (Table 2).

When stratified by outcome, patients with CVAE had significantly lower CO than those without CVAE (3.23 ± 0.8 vs 3.99 ± 1.1 L/min; p = 0.027). Similarly, CI was significantly lower in patients with CVAE than in those without CVAE (1.85 ± 0.4 vs 2.34 ± 0.7 L/min/m², p = 0.019). PAPi was also lower in patients with CVAE (0.56 [0.14–1.31]) than in patients without CVAE (1.35 [0.53–4.38]; p = 0.044). In contrast, no significant differences were observed in RAP, PAP, PCWP, RVSWI, PAC, RAP/PCWP, or PVR between patients with CVAE and patients without CVAE. Likewise, pulmonary hypertension subtypes were not significantly associated with outcome status (Table 2).

Table 2. Right heart catheterization hemodynamic parameters in patients with advanced heart failure according to CVAE status.

Variable	All patients (n=33)	Patients with CVAE (n=22)	Patients without CVAE (n=11)	P-value
RAP, mmHg	11.00 (6.50–18.00)	9.50 (6.75–18.00)	11.59 (6.00–23.00)	0.462
Mean PAP, mmHg	34.90 ± 9.1	35.18 ± 10.3	34.36 ± 6.6	0.812
PCWP, mmHg	22.79 ± 6.2	23.14 ± 6.3	22.09 ± 6.3	0.656
CO, L/min	3.48 ± 0.9	3.23 ± 0.8	3.99 ± 1.1	0.027
CI, L/min/m²	2.01 ± 0.6	1.85 ± 0.4	2.34 ± 0.7	0.019
RVSWI, g·m/m²/beat	561.00 (419.50–789.00)	586.12 (412.00–820.00)	554.00 (426.00–801.00)	0.807
PAPi, ratio	0.68 (0.16–1.61)	0.56 (0.14–1.31)	1.35 (0.53–4.38)	0.044
PAC, mL/mmHg	1.39 (1.05–2.47)	1.36 (0.97–1.78)	1.61 (1.11–2.86)	0.510
RAP/PCWP ratio	0.46 (0.27–0.79)	0.44 (0.27–0.66)	0.47 (0.23–1.00)	0.721
PVR, Wood units	3.89 ± 1.8	3.92 ± 1.7	3.86 ± 1.9	0.935
Pulmonary hypertension type, n (%)				0.637
Pre-capillary PH	0 (0.0)	0 (0.0)	0 (0.0)	
Isolated post-capillary PH	6 (18.2)	5 (22.7)	1 (9.1)	
Combined post- and pre-capillary PH	27 (81.8)	17 (77.3)	10 (90.9)	
RV dysfunction, n (%)	10 (30.3)	6 (27.3)	4 (36.4)	0.696

Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Units are shown in the variable column. CI, cardiac index; CO, cardiac output; CVAE, cardiovascular adverse event; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV, right ventricular; RVSWI, right ventricular stroke work index.

Table 3. Bivariate logistic regression analysis of right heart catheterization parameters associated with CVAE in patients with advanced heart failure.

Variable	OR (95% CI)	P-value
RAP, per 1 mmHg	1.075 (0.973–1.187)	0.156
Mean PAP, per 1 mmHg	1.010 (0.932–1.095)	0.805
PCWP, per 1 mmHg	1.029 (0.913–1.159)	0.254
CO, per 1 L/min	0.384 (0.171–0.987)	0.041
CI, per 1 L/min/m²	0.186 (0.038–0.911)	0.038
RVSWI, per 1 g·m/m²/beat	1.000 (0.999–1.002)	0.551
PAPi, per 1-unit increase	0.624 (0.393–0.977)	0.039
PAC, per 1 mL/mmHg	0.877 (0.467–1.618)	0.675
RAP/PCWP ratio, per 1-unit increase	3.652 (0.411–32.413)	0.245
PVR, per 1 Wood unit	1.045 (0.698–1.567)	0.830
Isolated post-capillary PH	2.941 (0.299–28.890)	0.355
Combined post- and pre-capillary PH	0.340 (0.035–3.340)	0.355

Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) from bivariate logistic regression. The outcome was CVAE. Because of the small sample size and limited number of events, the analyses should be interpreted as exploratory. CI, cardiac index; CO, cardiac output; CVAE, cardiovascular adverse event; PAC, pulmonary artery compliance; PAP, pulmonary artery pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index.

In bivariate logistic regression analysis, higher CO was associated with lower odds of CVAE (OR 0.384; 95% CI 0.171–0.987; p = 0.041). A similar association was observed for CI (OR 0.186; 95% CI 0.038–0.911; p = 0.038) and PAPi (OR 0.624; 95% CI 0.393–0.977; p = 0.039). Other hemodynamic parameters, including RAP, PAP, PCWP, RVSWI, PAC, RAP/PCWP, PVR, and pulmonary hypertension subtype, were not significantly associated with CVAE (Table 3).

Overall, these exploratory findings suggest that among selected patients with advanced heart failure who underwent RHC, lower forward-flow parameters, particularly CO and CI, as well as lower PAPi, were more closely associated with CVAE than isolated resting pressure-based or pulmonary vascular indices.

Discussion

In this two-center retrospective cohort of patients with advanced heart failure undergoing RHC, an important finding was the relatively young age profile of the study population. The mean age was 48.0 ± 11.3 years, which is younger than that reported in broader contemporary heart failure registries from both Asia and Western populations, including ASIAN-HF (59.6 ± 13.1 years), the Malaysian MY-HF registry (60.2 ± 13.6 years), the European ESC-HF-LT chronic heart failure registry (median age 66 years), and the U.S. ADHERE acute heart failure registry, in which the average age was approximately 73 years.[6-9] In parallel, ischemic cardiomyopathy was the predominant etiology in our study, accompanied by a substantial burden of smoking, hypertension, and diabetes. Taken together, these findings suggest that in our setting, progression to advanced heart failure severe enough to warrant invasive hemodynamic evaluation may occur at a relatively earlier age, potentially reflecting premature cardiovascular risk exposure and delayed referral until a more advanced stage of disease. The INTERMACS distribution further supports this interpretation, as most patients were classified as profile 4 and the remainder as profile 3, indicating that invasive evaluation was performed predominantly in patients with clinically advanced heart failure rather than in less symptomatic ambulatory individuals.[10]

The main finding of this cohort was that lower CO, CI, and PAPi were associated with CVAE, whereas conventional pressure-based variables such as RAP, PAP, PCWP, and PVR were not significantly associated with the outcome. Taken together, these findings suggest that in this cohort, markers of impaired forward flow and reduced right ventricular–pulmonary arterial pulsatile reserve may have been more closely related to subsequent clinical deterioration than congestion-related indices alone. This interpretation is in line with contemporary heart failure guidance and recent hemodynamic reviews, which emphasize that right heart catheterization provides prognostic information not only through absolute filling pressures, but also through indices of circulatory performance, right-sided adaptation, and overall hemodynamic reserve.[1,3-4]

Importantly, the lack of significant associations between pressure-based variables and CVAE in this cohort should not be misinterpreted as diminishing the clinical importance of congestion. Congestion is a major determinant of symptoms, hospitalization, and adverse prognosis in heart failure, and prior studies have demonstrated that persistent congestion is associated with worse outcomes, whereas successful decongestion is linked to improved survival. In this context, our results should be understood more cautiously that in a small, highly selected advanced heart failure population undergoing RHC, indices of impaired forward flow and reduced right-sided pulsatile reserve showed stronger discriminatory value than isolated resting pressure measurements, but this does not negate the central role of congestion in the natural history of heart failure.[13-14]

Advanced heart failure is characterized by the inability of the circulation to maintain adequate tissue perfusion without requiring pathologically elevated intracardiac pressures. Although congestion is a major determinant of symptoms and rehospitalization, impaired forward flow reflects a more advanced stage of hemodynamic compromise and may identify patients who are less able to tolerate additional clinical stressors. In routine advanced heart failure practice, low-output physiology is often accompanied by progressive end-organ dysfunction, recurrent decompensation, and greater vulnerability to shock, all of which may contribute to cardiovascular death or rehospitalization. Current guidance and contemporary reviews continue to recognize CO and CI as core hemodynamic parameters for risk assessment, particularly in advanced heart failure, cardiogenic shock, and evaluation for advanced therapies such as transplantation or mechanical circulatory support.[4,15]

Another finding was the association between lower PAPi and CVAE. PAPi has increasingly been used as an integrative marker of right ventricular

functional reserve and right ventricular adaptation to pulmonary vascular load. Although its optimal threshold varies by clinical setting, a lower PAPi is generally interpreted as reflecting impaired right ventricular pulsatile performance and a reduced ability of the right ventricle to maintain output under increased afterload. In advanced heart failure, this may be particularly relevant because deterioration of right ventricular function often signals a more unstable hemodynamic state, greater systemic venous congestion, and poorer tolerance of acute decompensation. Recent reviews on invasive hemodynamic assessment in heart failure have highlighted PAPi as a potentially useful adjunct beyond traditional pressure measurements, especially in advanced heart failure and shock-related settings. [3,5,15] Our findings support the relevance of PAPi even in a small, real-world Indonesian cohort undergoing selective invasive evaluation.

By contrast, RAP, PAP, PCWP, PVR, PAC, RVSWI, and RAP/PCWP were not significantly associated with CVAE in this study. This should not be interpreted as evidence that these variables are clinically unimportant. Rather, several explanations are possible. First, the sample size was small, which limits statistical power. Second, this was a selected referral population from two tertiary centers, and the relatively narrow hemodynamic range of some variables may have reduced discriminatory capacity. Third, pressure-based variables often reflect a single moment in time and can be influenced by loading conditions, timing of measurement, and ongoing treatment. In contrast, output-related variables and composite indices, such as PAPi, may better reflect the overall severity of circulatory dysfunction. Contemporary hemodynamic literature likewise emphasizes that right heart catheterization should be interpreted as a physiological profile rather than as isolated numbers.[3-5]

In our study, pulmonary hypertension subtype was also not significantly associated with the composite outcome. This may be explained, at least in part, by the fact that most patients had combined post- and pre-capillary pulmonary hypertension, leaving limited variation for meaningful between-group comparison. In addition, the clinical impact of pulmonary hypertension in advanced heart failure depends not only on resting invasive classification, but also on chronicity, right ventricular adaptation, and treatment context. Therefore, the lack of statistical significance in this cohort should be interpreted with caution and not taken as proof of no clinical relevance. More likely, it reflects the limited sample size and the relatively homogeneous hemodynamic severity of this referral population.[1, 15]

The present findings are relevant in the Indonesian setting, where access to right heart catheterization in advanced heart failure remains limited to a small number of tertiary centers. In such settings, even descriptive data are valuable because they provide insight into the hemodynamic phenotype of patients selected for invasive evaluation. Our results suggest that among these patients, forward-flow indices may be more informative than pressure-derived variables alone when identifying those at higher risk of cardiovascular death or rehospitalization. From a practical perspective, this supports careful attention to CO, CI, and PAPi when interpreting invasive hemodynamic data in advanced heart failure, while recognizing that treatment decisions must still be based on the overall clinical context rather than on a single parameter. Clinically, patients with low CO, low CI, or reduced PAPi may require closer follow-up, optimization of advanced heart failure therapy, and timely multidisciplinary discussion regarding candidacy for LVAD implantation, heart transplantation, or palliative-oriented management when advanced therapies are not feasible. However, these parameters should not be used as standalone thresholds, and treatment decisions must remain individualized according to the overall clinical context. [1,3-4,15]

The baseline treatment and advanced heart failure status data further support the interpretation that this was a clinically high-risk referral cohort. Although most patients were receiving ACEi/ARNI, mineralocorticoid receptor antagonists, and loop diuretics, the relatively low use of beta-blockers, SGLT2 inhibitors, and device therapy likely reflects the severity, instability, and treatment constraints that commonly accompany advanced heart failure in routine practice. In addition, a substantial proportion of patients were categorized as candidates for heart transplantation or LVAD, while one-fifth were already considered unsuitable for advanced therapy. These findings help contextualize the observed event rates and suggest that invasive hemodynamic assessment in this cohort was performed not only for diagnostic profiling but also as part of broader advanced heart failure decision-making.[1,4,16]

Limitations and Strengths

Several limitations should be acknowledged. First, this was a retrospective study and is therefore subject to information bias and unmeasured confounding. Second, the study included only

patients who underwent clinically indicated RHC, representing a highly selected and high-risk advanced heart failure population. This selection limits generalizability to broader heart failure populations that do not undergo invasive hemodynamic assessment. Accordingly, the findings should be considered exploratory and hypothesis-generating. Third, the composite outcome combined cardiovascular death and rehospitalization due to several causes of decompensation, which improves clinical relevance but may introduce heterogeneity in event mechanisms. Finally, because the analysis was limited to descriptive comparisons and bivariate logistic regression, the present study cannot establish independent predictors or causal relationships.

Despite these limitations, this study has several strengths. It provides one of the few descriptions of invasive hemodynamic characteristics in patients with advanced heart failure from two tertiary Indonesian centers, and evaluates clinically meaningful outcomes using routinely obtained RHC variables. Importantly, the observed pattern was physiologically coherent: adverse events were associated primarily with lower output-related parameters and lower PAPi rather than with uniformly higher pressure-based measurements. This internal consistency supports the clinical plausibility of the findings, even within a modest sample.

Future Direction

Future studies should include larger prospective multicenter cohorts to validate the prognostic significance of invasive hemodynamic parameters in advanced heart failure. Broader recruitment would improve generalizability and allow more robust adjusted analyses to determine whether CO, CI, and PAPi remain associated with adverse outcomes after accounting for clinical confounders. Serial hemodynamic assessment, integrated with echocardiographic and laboratory markers, may also provide a more comprehensive strategy for risk stratification. In the Indonesian setting, expanding local data on RHC may help refine its role in identifying high-risk patients with advanced heart failure and in guiding clinical decision-making.

Conclusion

In this two-center retrospective cohort of patients with advanced heart failure undergoing clinically indicated RHC, lower CO, lower CI, and lower PAPi were associated with CVAE. Because of the small sample size and selected RHC population, these findings should be interpreted as exploratory and hypothesis-generating. Larger prospective multicenter studies are needed to validate whether these parameters improve risk stratification beyond routine clinical assessment.

List of Abbreviations

ACEi	Angiotensin-Converting Enzyme
ARNI	Angiotensin Receptor–Neprilysin inhibitor
CO	Cardiac Output
CI	Cardiac Index
CIs	Confidence Intervals
CRT	Cardiac Resynchronization Therapy
CVAE	Cardiovascular Adverse Events
ICD	Implantable Cardioverter-Defibrillator
IQR	Interquartile Range
LAVI	Left Atrial Volume Index
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
OR	Odds Ratios
PAC	Pulmonary Artery Compliance
PAP	Pulmonary Artery Pressure
PAPi	Pulmonary Artery Pulsatility index
PCWP	Pulmonary Capillary Wedge Pressure
PVR	Pulmonary Vascular Resistance
RAP	Right Atrial Pressure
RHC	Right Heart Catheterization
RVSWI	Right Ventricular Stroke Work Index
TRVmax	Tricuspid Regurgitation Maximum velocity

Ethical Clearance

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of National Cardiovascular Center Harapan Kita, Jakarta (protocol no LB.02.01A/II/028/KEP028/2023) and Dr. Hasan Sadikin General Hospital, Bandung (protocol no. KP.04.04/D.XIV.3.4.23/271/2025). Because this study involved a retrospective analysis of anonymized registry data, the ethics committee waived the requirement for informed consent.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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Copyright/Permissions for Figures

Not applicable.

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Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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Review Article

Impact of Cardiac Contractility Modulation on Left Ventricular Ejection Fraction and Clinical Outcomes in Heart Failure: A Systematic Review and Meta-Analysis

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Abstract

Patients with heart failure and narrow QRS often remain symptomatic despite Optimal Medical Therapy (OMT), while CRT is usually not indicated. Cardiac Contractility Modulation (CCM) may improve symptoms and quality of life in this population. This systematic review and meta-analysis included studies comparing CCM to either OMT alone or OMT with CRT. Assessed outcomes included improvements in clinical, structural, and physiological domains. Random-effects models were applied for all analyses, and results were reported as Odds Ratios (OR) or Mean Differences (MD) with 95% Confidence Intervals (CI). All statistical analyses were conducted using Review Manager V.5.4. A total of eight studies involving 1,486 patients with heart failure were included in this analysis. In terms of structural outcomes, CCM demonstrated improvements in LVEF comparable to those of CRT, with no statistically significant difference between the two therapies ($p>0.05$). Compared to the OMT-only group, CCM showed significantly greater improvements in VO_2 max (MD 0.91; 95%CI 0.44-1.37; $p<0.001$; $I^2=33\%$), 6MWD (MD 17.95; 95% CI 5.45-30.45; $p=0.005$; $I^2=0\%$), and MLHFQ (MD -7.56; 95% CI -11.65 to -3.47; $p<0.001$; $I^2=39\%$). Although no significant differences were observed between CCM and control in terms of all-cause mortality, MACE, or rehospitalization ($p>0.05$), CCM group showed significant improvements in quality of life, as measured by NYHA functional class (MD 2.74; 95%CI 1.47-5.12; $p<0.001$; $I^2=76\%$). CCM is a promising therapy for heart failure, offering structural benefits comparable to CRT in narrow QRS patients and improving function and quality of life beyond OMT, despite no significant reduction in hard clinical outcomes.

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Keywords: Device based therapy, Cardiac resynchronization therapy, Cardiac contractility modulation, Heart failure, Optimal medical therapy

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Introduction

Despite major advancements in pharmaceutical therapy, heart failure remains a significant worldwide public health burden, marked by high rates of morbidity, death, and hospitalization. According to current estimates, millions of people worldwide suffer from heart failure, and as the population ages and survival rates from acute cardiovascular problems improve, the prevalence of heart failure continues to climb. A substantial percentage of patients with Heart Failure with reduced Ejection Fraction (HFrEF) continue to experience symptoms, recurrent hospitalizations, and progressive myocardial deterioration despite optimal guideline-directed medical therapy, such as neurohormonal blockade and more recent disease-modifying medications. This ongoing clinical load emphasizes the necessity of treatment approaches that go beyond pharmaceutical optimization.[1-2]

Device-based therapies are indicated for patients who continue to have symptoms after receiving Optimal Medical Therapy (OMT). Cardiac Resynchronization Therapy (CRT) is one of these devices; in patients with heart failure and Left Ventricular (LV) systolic dysfunction accompanied by electrical dyssynchrony, it improves symptoms, hospitalization rates, and survival. However, approximately 30% of patients do not show adequate response, and its application is not recommended in individuals with a QRS duration of less than 120 milliseconds. Therefore, even with OMT, the majority of heart failure patients remain symptomatic and ineligible for CRT.[1–3]

This therapeutic gap can be filled by Cardiac Contractility Modulation (CCM), which does not require electrical resynchronization. By delivering high-voltage, biphasic, non-excitatory electrical impulses during the absolute refractory phase, CCM improves myocardial contractility by modulating gene expression and calcium handling, thereby enhancing contraction without increasing myocardial oxygen demand. Because of this QRS-independent mechanism, CCM is a good choice for patients who are not candidates for or respond poorly to CRT.[2-3]

In patients with heart failure and reduced ejection fraction who continue to experience symptoms while receiving OMT, CCM has consistently demonstrated improvements in functional capacity, quality of life, New York Heart Association functional class, and Left Ventricular Ejection Fraction (LVEF). Notably, the data suggest a specific advantage for individuals with a narrow QRS duration and an intermediate LVEF — a population for which there have traditionally been few treatment options. As an adjunctive device-based therapy, CCM is increasingly being incorporated into modern heart failure treatment algorithms as a result of these findings, which have led to regulatory approval in several regions.[2-3]

In light of these recent findings, this systematic review and meta-analysis aim to evaluate the effects of CCM in patients with heart failure, with a particular focus on structural and functional parameters and clinical endpoints, clarifying its role within the modern heart failure therapeutic landscape.

Methods

Study Design and Protocol Registration

The study design of this meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5.[4-5] The study protocol was registered in PROSPERO with the registration number CRD420251273539.

Search Strategies

A systematic literature search was carried out comprehensively through seven different databases, including PubMed, Embase, and Cochrane Library, up until March 2025. The search strategy employed boolean operator with the following keywords: [("Heart Failure" OR "HF") AND ("CCM" OR "Cardiac Contractility Modulation") AND ("Optimal Medical Therapy") AND ("CRT" OR "Cardiac Resynchronization Therapy") AND ("randomized control trial" OR random OR randomized OR randomized OR RCT)]. All terms were aligned with the MeSH (Medical Subject Headings).

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria were predefined prior to the literature search to ensure the homogeneity and methodological rigor of the included studies. Studies were eligible for inclusion if they met the following criteria: (1) study focuses on adult patients aged more than or equal to 18 years old with documented heart failure with a New-York Heart Association (NYHA) functional class of 2 or above, (2) evaluated CCM as the intervention (3) used optimal medication therapy alone or combined with CRT as the control group, (4) reported primary outcomes surrounding clinical parameters such as, NYHA functional class, Major Adverse Cardiovascular Event (MACE), and all-

cause mortality, with or without secondary outcomes such as LVEF, rehospitalization, 6-Minute Walk Distance (6MWD), Minnesota Living with Heart Failure Questionnaire (MLHFQ), and VO_2max. Studies were excluded if the corresponding authors did not respond to full-text requests after two contact attempts. No restrictions were placed on the publication date. Study eligibility was independently assessed by the authors, and any discrepancies were resolved through discussion and consensus.

Screening and Data Extraction

Database screening was independently conducted by two reviewers (INW and DY), and any conflicts were resolved by a third reviewer (GNPJ). Duplicate studies were removed manually. Eligible studies were extracted and organized into a Microsoft Excel 2021 spreadsheet. Additional data, including country, number of participants, gender distribution, and specifics of the intervention, were also collected. Study characteristics and outcomes were assessed qualitatively by two reviewers (DY and PJ), while NKAD and CAS reviewed the extracted data for accuracy and performed statistical analyses.

Qualitative Appraisal

Risk of bias was assessed using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0). This evaluation was applied to all studies included in the meta-analysis, following the standardized methodology developed by the Cochrane Collaboration. Two authors (INW and DY) independently conducted the assessments, and any discrepancies were resolved by the third reviewer (GNPJ). The results were recorded in a structured spreadsheet (.xlsx) and uploaded to the ROBVIS tool to generate visual summaries of the risk of bias. A traffic light plot was used to display the domain-specific and overall risk assessments.

Quantitative Analysis

The meta-analysis was performed using RevMan 5.4. Primary outcomes were analyzed as mean differences, while secondary outcomes were analyzed as Odds Ratios (OR) with their respective 95% Confidence Intervals (95% CI). All analyses were conducted using a random-effects model. An additional funnel plot will be generated to assess small-study bias, with an additional Egger's test only when at least 10 studies are available.

Results

Study Selection

Through database searches of PubMed, Embase, and the Cochrane Library, 196 entries were found. There were 158 unique items left for screening after 38 duplicate data points were eliminated. 131 items were eliminated during the title and abstract screening process because they dealt with unrelated subjects, animal research, or editorial-style publications. The eligibility of twenty-seven full-text publications was then evaluated. Nineteen of these studies were eliminated due to the lack of a comparator group, inadequate outcome data (n = 10), duplicate populations and overlapping datasets (n = 3), or non-original study designs, such as case reports or reviews (n = 6). Eight articles were ultimately included in the systematic review and meta-analysis after meeting the inclusion criteria. Figure 1 provides a more detailed explanation.

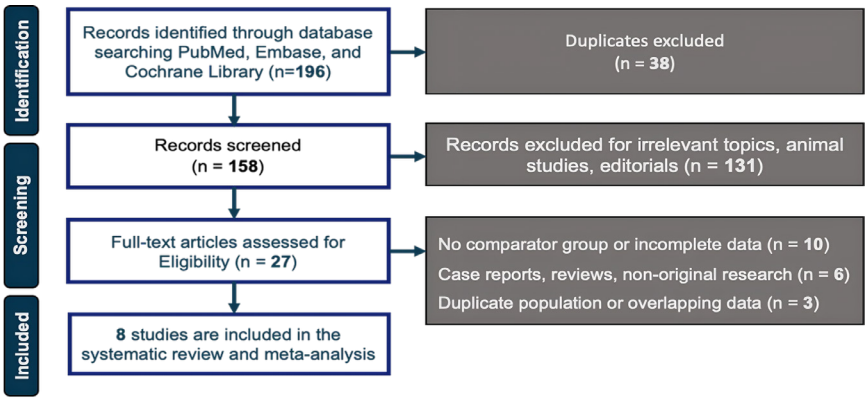

Figure 1. PRISMA chart.

Risk of Bias

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias tool version 2.0 (RoB 2.0) for the 5 Randomized Controlled Trials (RCTs), and the 3 cohorts were assessed using the Newcastle Ottawa Scale (NOS) tool, with the detailed judgments summarized in Figure 2 and Figure 3, respectively. The randomized clinical trial included in this meta-analysis showed a low risk across all RoB2 domains, including the randomization process, blinding, deviations from the intended intervention, missing outcome data, appropriate measurements, and reporting results. The cohorts also showed a similar low risk of bias according to the NOS, based on their selection protocols, sample comparability, and assessment of study outcomes.

Characteristics of Included Studies

A total of eight studies were analyzed; these studies comprised of five RCTs, with three cohorts. Sample sizes varied across studies, with CCM groups ranging from 25 to 215 participants and control groups from 24 to 220 participants. Most studies enrolled patients with HFrEF, while several included mixed populations with Heart Failure with mildly reduced Ejection Fraction (HFmrEF). Across trials, most participants were male and classified as New York Heart Association functional class III–IV. Notably, two studies used CRT combined with OMT as the control group, whereas the remaining studies employed OMT alone as the comparator. Follow-up duration ranged from 12 to 72 weeks. Most studies consistently reported background medical

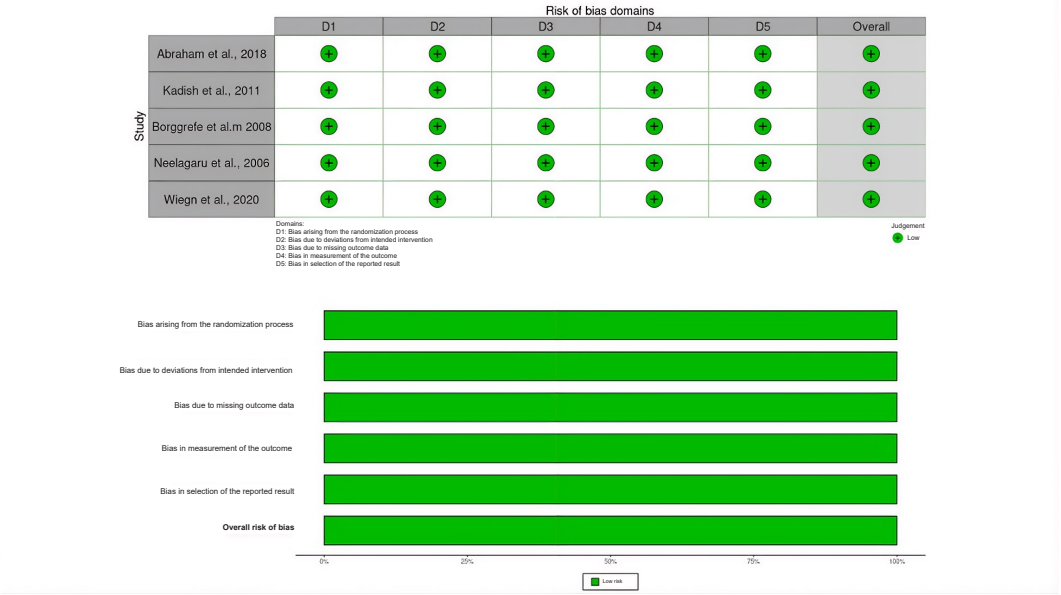

Figure 2. Traffic light plot depicting risk of bias assessment summarizing the risk of bias evaluation for the included studies using Revised Risk of Bias in Randomized Trials 2 tool.

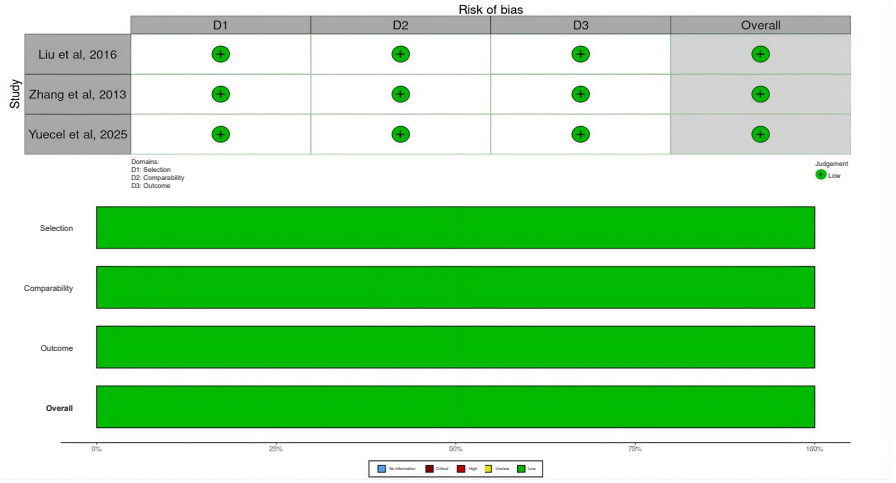

Figure 3. Traffic light plot depicting risk of bias assessment summarizing the risk of bias evaluation for the included studies using Newcastle Ottawa Scale tool.

therapy, which frequently included beta-blockers, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors, diuretics, and sodium–glucose cotransporter-2 inhibitors. More detailed baseline characteristics can be viewed in Table 1.

NYHA functional class improvement

The analysis of NYHA functional class improvement includes three RCTs and two cohort studies. 574 patients were in the control group, and 404 patients were in the CCM group. The random-effects meta-analysis showed a higher likelihood of increasing NYHA functional class by up to 174% than the control group, with a pooled OR of 2.74 (95% confidence range of 1.47 to 5.12; p = 0.002). This result is similar across the subgroups comparing CCM with OMT and CCM with CRT; the corresponding pooled ORs were 4.17 (95% CI of 1.92 to 9.07) and 1.52 (95% CI of 0.88 to 2.63). With an I^2 value of 76% (τ^2 = 0.44; p = 0.001) for the overall pooled effect and 72% (τ^2 = 0.34; p = 0.03) for the CCM vs. OMT pooled effect, there was significant heterogeneity aside from the subgroup analysis between CCM and CRT. Conversely, CCM vs. CRT only displayed an I^2 value of 26% (τ^2 = 0.07; p = 0.26), which is not statistically significant. Except for the CCM vs. CRT subgroup (p = 0.26), both the overall pooled effect (p = 0.001) and the CCM vs. OMT subgroup pooled effect (p = 0.03) are statistically significant. The corresponding forest plot result is shown in Figure 4.

Table 1. Baseline characteristics.

Author	Design	CCM (n)	Control (n)	Type of Control	Mean QRS duration (SD)	Mean LVEF% (SD)	Male (%)	Mean Age (SD)	Follow-up (weeks)
Yuecel et al. 2025[6]	Cohort	105	220	OMT+CRT	141.2 (28.2)	25.4 (6.5)	78,4	67.2 (11.7)	52
Wiegn et al., 2020[7]	RCT	60	86	OMT	102.6 (12.2)	33.2 (5.6)	82,8	64.2 (11.2)	24
Abraham et al. 2018[8]	RCT	191	198	OMT	103.3 (12.49)	33.0 (5.4)	76,2	63.0 (11.0)	24
Zhang et al. 2012[9]	Cohort	33	99	OMT+CRT	139.4 (30.9)	26.6 (8.0)	71,2	63.8 (1.9)	72
Kadish et al. 2011[10]	RCT	215	213	OMT	101.6 (14.1)	25.9 (6.5)	71,9	58.3 (12.5)	12
Borggrefe et al. 2008[11]	RCT	80	84	OMT	118.1 (27.7)	29.5 (7.2)	84,7	59.4 (9.9)	50
Neelagaru et al. 2006[12]	RCT	25	24	OMT	105.9 (15.4)	28.1 (7.6)	69,3	57.0 (14.1)	24
Liu et al. 2016[13]	Cohort	41	41	OMT	<130	27.0 (6.5)	85,3	62.5 (10.6)	24

RCT: Randomized Controlled Trials; OMT: Optimal Medical Therapy; LVEF: Left Ventricular Ejection Fraction; SD: Standard Deviation.

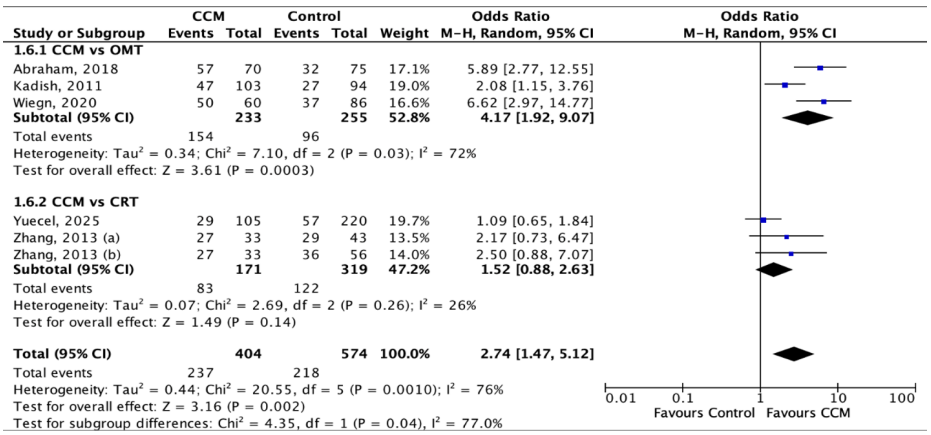

Figure 4. Forest plot depicting the subgroup analysis for NYHA functional class.

All-Cause Mortality

The analysis of all-cause mortality included five RCTs and two cohort studies, including 750 patients in the control group and 592 patients in the CCM group. CCM has a lower all-cause mortality rate than OMT, with or without RCTs, as evidenced by a 25% lower odds of all-cause mortality, according to the random-effects meta-analysis, which reported a pooled OR of 0.75 (95% CI, 0.35 to 1.61). With an I^2 score of 46% (τ^2 = 0.43; p = 0.08), between-

study heterogeneity was moderate. Nevertheless, the outcome (p = 0.47) was not statistically significant. The corresponding forest plot result is shown in Figure 5.

Further sensitivity analysis was performed, in which only five RCTs, including 446 patients in the CCM group and 489 in the control group, were considered to reduce heterogeneity. CCM here did not show a lower all-cause mortality rate compared to the control, as indicated by the pooled OR of 0.95 (95% CI of 0.35 to 1.61; p = 0.89). Heterogeneity is lower than in the previous pooled result, with an I^2 score of 0% (τ^2 = 0.00; p = 0.52). However, both the summary effect and the heterogeneity in this analysis have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 6.

Major Adverse Cardiovascular Events

The MACE analysis included five RCTs and one cohort study with 563 patients in the CCM group and 709 patients in the control group. The CCM group had a higher overall incidence of MACE, with an odds ratio 58% higher than the control group, according to the pooled effect estimate, yielding an OR of 1.58 (95% CI of 0.85 to 2.93). With an I^2 score of 67% (τ^2 = 0.38; p = 0.01), between-study heterogeneity was moderate to high. The overall effect was not statistically significant (p = 0.15), even though the direction of effect indicated a higher incidence of MACE in the CCM group. The corresponding forest plot result is shown in Figure 7.

Further sensitivity analysis was conducted on five RCTs along with 458 patients in the CCM group and 489 patients in the control group. The CCM still showed a higher MACE incidence, with a pooled OR of 1.28 and a 95% CI of 0.83 to 1.96 (p = 0.27). Heterogeneity has dropped to an I^2 score of 0% (τ^2 = 0.00; p = 0.52). Both the summary effect and the heterogeneity in this analysis, however, have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 8.

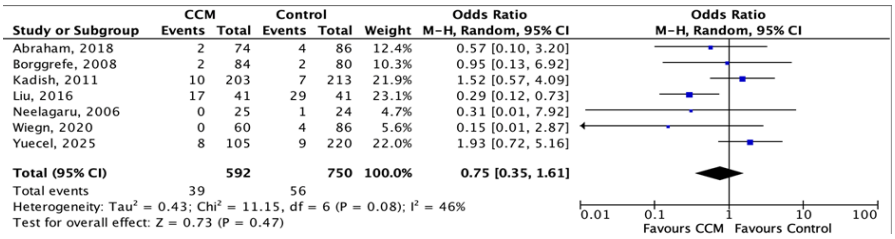

Figure 5. Forest plot depicting the analysis for all-cause mortality event.

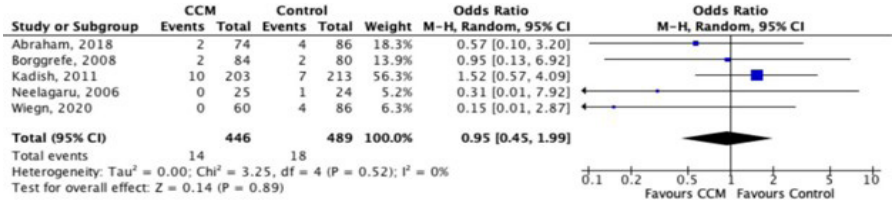

Figure 6. Forest plot depicting the sensitivity analysis of all-cause mortality event.

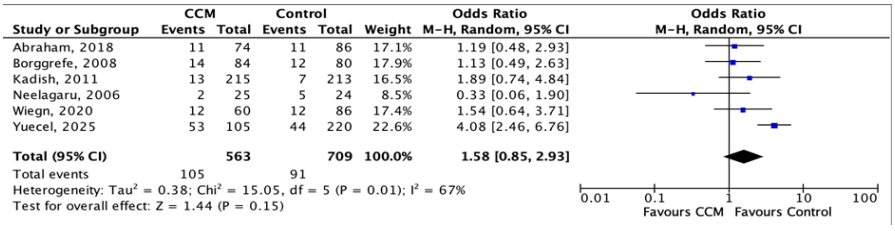

Figure 7. Forest plot depicting the major adverse cardiovascular event.

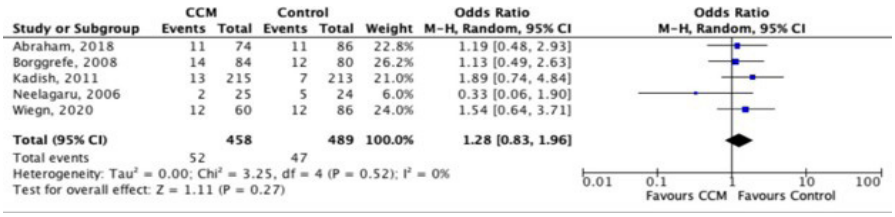

Figure 8. Forest plot depicting the sensitivity analysis of major adverse cardiovascular event.

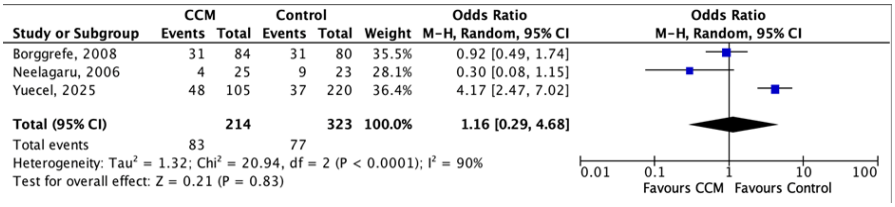

Figure 9. Forest plot depicting the analysis of the rehospitalization event.

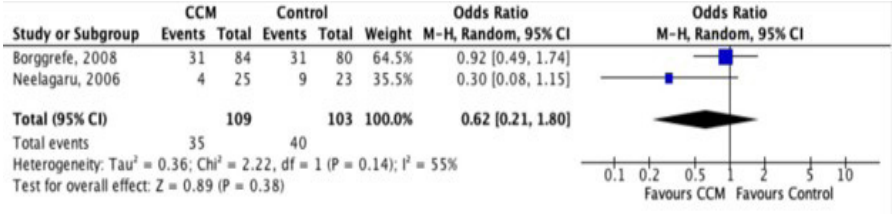

Figure 10. Forest plot depicting the sensitivity analysis of the rehospitalization event.

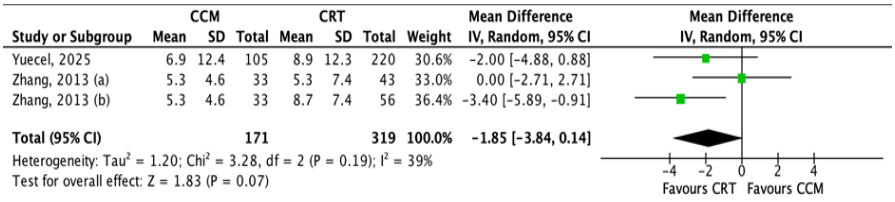

Figure 11. Forest plot depicting the left ventricular ejection fraction.

Rehospitalization

The heart failure-related rehospitalization analysis included two RCTs and one cohort study, comprising 323 patients in the control group and 214 in the CCM group. CCM was associated with a 16% higher risk of rehospitalization compared with the control group, according to a pooled OR of 1.16 (95% CI of 0.29 to 4.68). With an I^2 value of 90% ($\tau^2 = 1.32$; $p < 0.0001$), significant heterogeneity was observed among trials, indicating substantial variation in impact estimates. However, $p = 0.83$ indicated that this was not statistically significant. The corresponding forest plot result is shown in Figure 9.

Further sensitivity analysis was conducted, which included 2 RCTs along with 109 patients in the CCM group and 103 patients in the control group. CCM here showed a different direction of effect, where it is associated with a lower rehospitalization compared to the control group, with a pooled OR of 0.62 and a 95% CI of 0.21 to 1.80 ($p = 0.38$). Heterogeneity here is lower than the previous result, with an I^2 score of 55% ($\tau^2 = 0.36$; $p < 0.14$). Both the summary effect and the heterogeneity in this analysis, however, have failed to reach statistical significance. The corresponding forest plot result is shown in Figure 10.

Left Ventricular Ejection Fraction

The analysis of left ejection fraction improvement included three cohort studies, including 319 patients in the OMT+CRT group and 171 patients in the CCM group. A decreased LVEF in CCM was shown by the random-effects meta-analysis, with a pooled mean difference of -1.85 and a 95% CI of -3.84 to 0.14. With an I^2 score of 39% ($\tau^2 = 1.20$; $p = 0.19$), there was little between-study heterogeneity. This result was not statistically significant ($p = 0.07$). The corresponding forest plot is shown in Figure 11.

6-Minute Walk Distance

The study of 6MWD improvement included four RCTs with 339 patients in the OMT group and 360 in the CCM group. A positive improvement in 6MWD with CCM over control was shown by the random-effects meta-analysis; the pooled mean difference was +17.95 meters, with a 95% CI of 5.45 to 30.45. There was no evidence of between-study heterogeneity (I^2 = 0%; τ^2 = 0.00; p = 0.63). A statistically significant overall impact was seen (p = 0.005). The corresponding forest plot is shown in Figure 12.

Peak Oxygen Consumption (VO_2 Max)

Peak oxygen consumption was analyzed from five RCTs, including 408 patients in the OMT group and 401 patients in the CCM group. The CCM group had a greater peak oxygen consumption, according to the random-effects meta-analysis, with a mean difference of +0.91 mL/kg/min and a 95% CI of 0.44 to 1.37. The I^2 score was 61% (τ^2 = 9.93; p = 0.08), indicating low between-study heterogeneity. A statistically significant overall impact was seen (p = 0.01). The corresponding forest plot is shown in Figure 13.

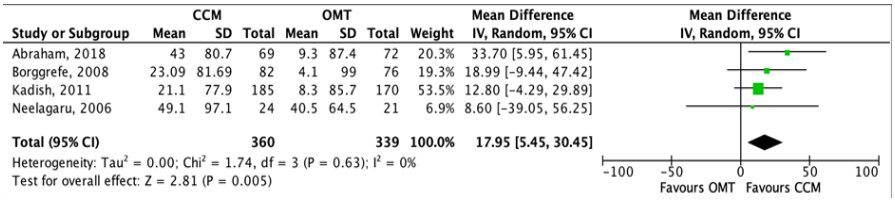

Figure 12. Forest plot depicting the 6-minute walk distance.

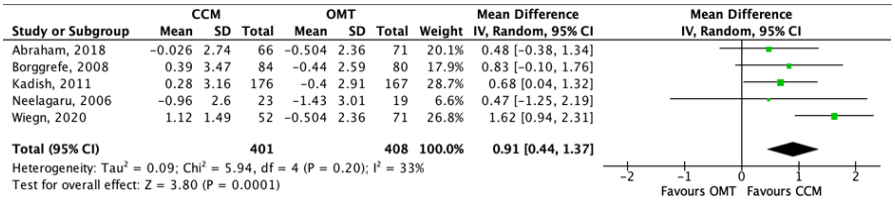

Figure 13. Forest plot depicting the VO_2 Max.

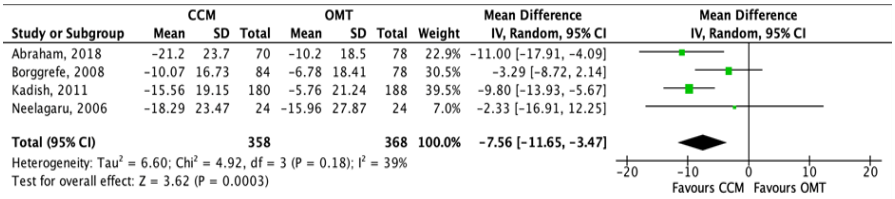

Figure 14. Forest plot depicting the MLHFQ score

Minnesota Living with Heart Failure Questionnaire

The MLHFQ analysis included four RCTs, with 358 patients in the CCM group and 363 patients in the OMT group. The pooled mean difference was -7.56 points, with a 95% CI of -11.65 to -3.47. This indicates that the CCM group had a lower questionnaire score on average than the control group, which is indicative of a higher quality of life. The I^2 score was 39% (τ^2 = 6.60; p = 0.18), indicating minimal between-study heterogeneity. The heterogeneity results were not statistically significant, even though the total impact was (p = 0.0003). The corresponding forest plot is shown in Figure 14.

Funnel Plot

Overall, asymmetry can be observed for most, if not all, efficacy outcomes. This can be explained by the low number of studies that were included and an even smaller number of included studies for some of the variables. However, the risk of small study bias is low due to most studies having large samples, even if they are clustered in favor of certain outcomes. Risk of publication bias, on the other hand, is still very much a possibility; this is supported by the overwhelming agreement between most, if not all, the studies in their respective variables. Funnel plots mentioned are presented in Figure 15.

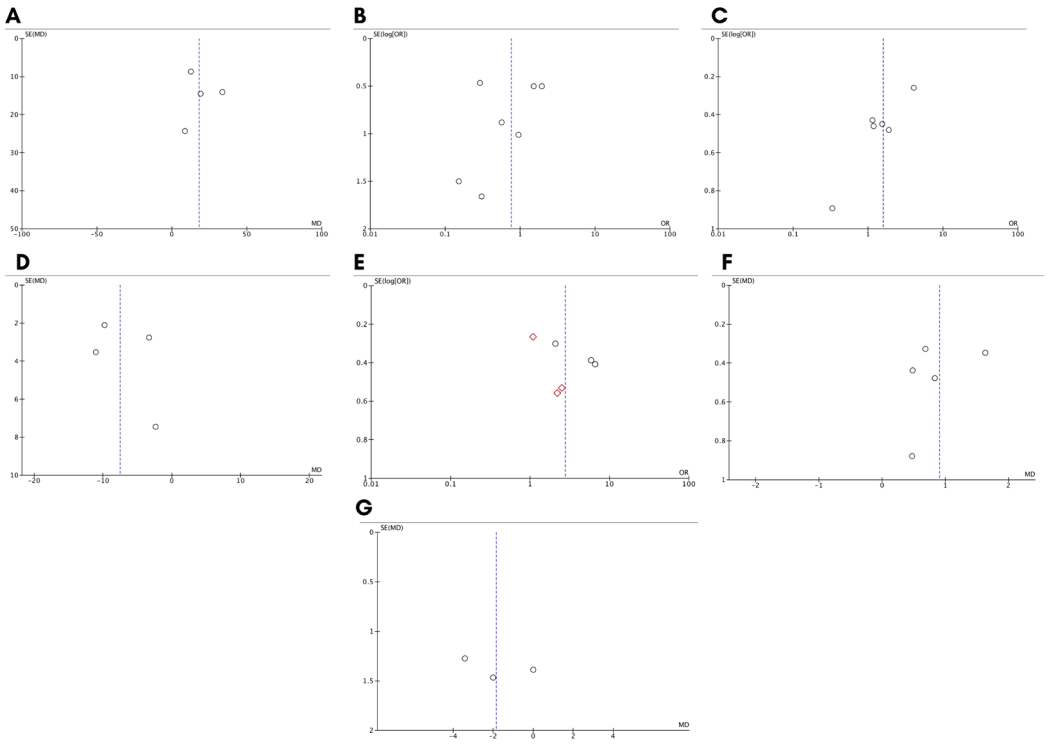

Figure 15. Corresponding funnel plots for 6-minute walk distance (A), all-cause mortality (B), major adverse cardiovascular event (C), Minnesota Living with Heart Failure Questionnaire (D), NYHA functional class (E), VO2 MAX (F), and LVEF (G).

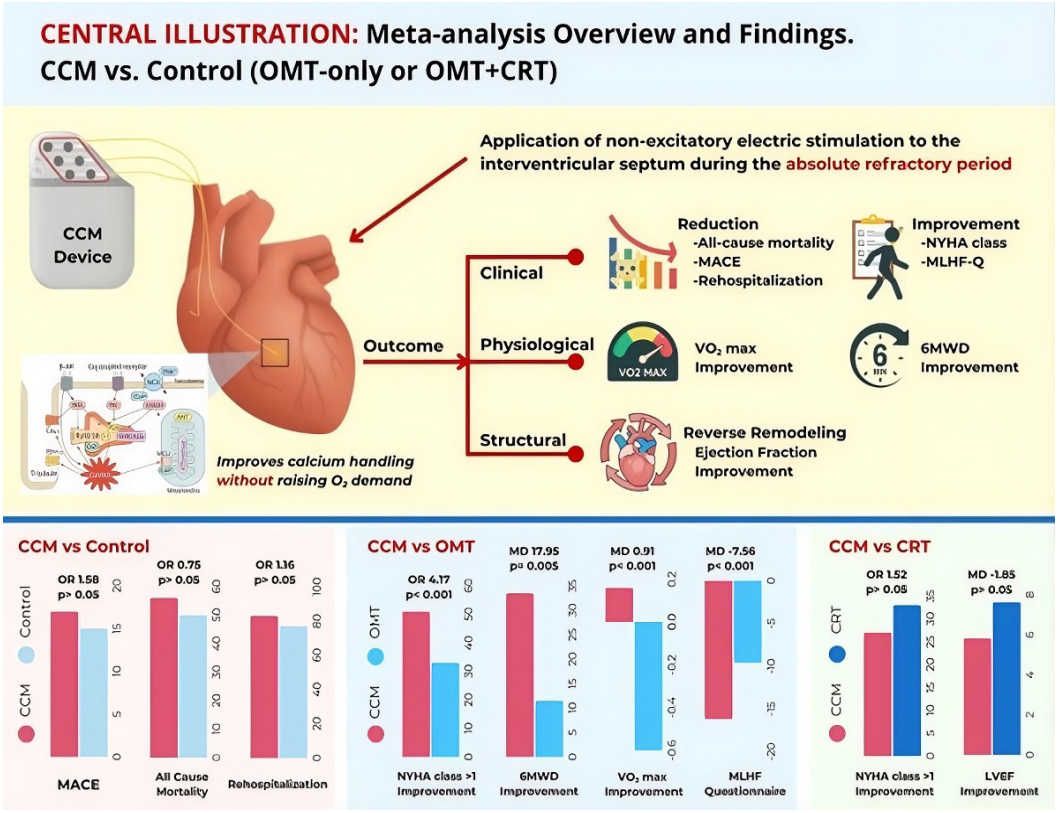

Figure 16. Overview of different comparators and their respective findings.

Discussion

This meta-analysis shows that CCM consistently improves clinical and physiological outcomes in heart failure, with statistically significant gains across NYHA functional class, 6MWD, peak oxygen consumption, and quality of life. CCM demonstrates no statistically significant difference when compared to CRT in improving functional status, with both therapies performing comparably. The significant improvement observed in the overall analysis is primarily driven by comparisons with OMT, as seen in Figure 16, whereas no statistically significant difference was observed between CCM and CRT. This finding suggests that CCM effectively improves symptoms to a degree similar to CRT in appropriately selected patients, particularly those who are not candidates for resynchronization therapy.

Physiological capacity and quality of life consistently favored CCM. CCM improved exercise tolerance to a significant degree, as reflected by better performance on the 6MWD test and increased peak oxygen consumption compared with OMT alone. In addition, CCM improved the quality of life, with patients reporting better scores on validated heart failure questionnaires by around eight points. These findings were generally consistent across studies, supporting the robustness of CCM's effect on functional and patient-reported outcomes.

In contrast, all-cause mortality, MACE, and rehospitalization were not significantly reduced with CCM. Notably, the point estimate for MACE trended in an unfavorable direction, and rehospitalization demonstrated extreme between-study heterogeneity, limiting interpretability. Heterogeneity in the MACE analysis was largely driven by the study by Yuecel et al.[6], in which the CCM group experienced worse outcomes compared with CRT-D. Importantly, this study enrolled a population with lower baseline ejection fraction and a higher burden of ventricular arrhythmias, both of which are strongly associated with poorer prognosis.[14] When this study was excluded, heterogeneity resolved and the MACE point estimate attenuated, yet the overall effect remained non-significant, suggesting that population differences rather than a deleterious effect of CCM accounted for the observed signal.

A further consideration of fundamental importance is that CCM and CRT are not applied to identical patient populations, and direct comparative interpretation must account for this distinction. CRT is an established device therapy with a primary indication in patients with wide QRS complexes, where the underlying pathophysiology is one of electrical dyssynchrony. CCM, by contrast, is typically indicated in patients with narrow QRS duration who are not candidates for CRT, a population in which heart failure is driven predominantly by intrinsic myocardial contractile impairment rather than dyssynchrony. Viewed in this context, the clinical significance of our findings is that CCM achieves comparable structural outcomes to CRT despite being applied in a population that is inherently less responsive to resynchronization-based interventions, reinforcing the value of CCM as a complementary therapy targeting a distinct and underserved patient population.

The differential roles of CCM and CRT are further clarified when considered within the framework of electrical conduction. In patients with wide QRS duration, mechanical dyssynchrony is the dominant abnormality, and CRT improves outcomes by restoring coordinated ventricular contraction. In contrast, patients with narrow QRS duration typically have preserved electrical synchrony, with heart failure driven primarily by impaired myocardial contractile strength[18], as illustrated in Figure 17. Current guidelines provide strong indications for CRT in patients with reduced ejection fraction and prolonged QRS duration, whereas patients with narrow QRS are often limited to implantable cardioverter-defibrillator therapy for sudden death prevention, which does not address symptoms or myocardial dysfunction. In this context, CCM may fill an important role, particularly in patients with narrow QRS duration and ejection fraction above traditional CRT thresholds.[19]

Regarding structural outcomes, ejection fraction alone is an incomplete surrogate for structural recovery in the context of CCM. Unlike CRT, which improves Ejection Fraction (EF) partly through geometric resynchronization of a dyssynchronous ventricle, CCM acts on calcium handling and myocyte contractility globally, a mechanism that may produce meaningful structural benefit without necessarily driving large shifts in ejection fraction. The comparable LVEF between CCM and CRT observed in this analysis should therefore be interpreted not as evidence of a failure of CCM to achieve structural benefit, but as evidence that CCM achieves equivalent structural outcomes in a population in which CRT's geometric advantage does not apply. This interpretation is supported by echocardiographic data demonstrating uniform augmentation of LV systolic function, reduction in functional mitral regurgitation, and favorable

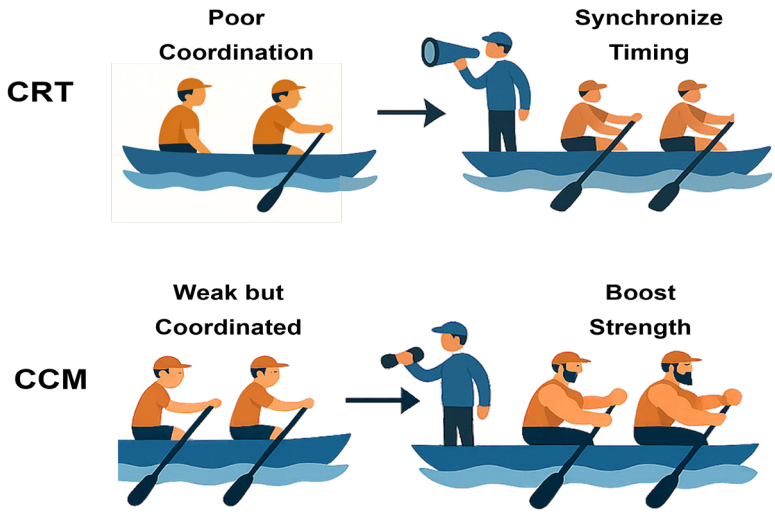

Figure 17. A comparison of the mechanism of action between CCM and CRT.

structural adaptation — effects not fully captured by ejection fraction alone and that collectively reflect meaningful myocardial recovery.[16]

These structural and functional effects align with the underlying mechanisms of CCM. In heart failure, impaired calcium handling due to reduced Sarco/Endoplasmic Reticulum Calcium ATPase (SERCA) activity, persistent phospholamban inhibition, downregulation of L-type calcium channels, and altered mitochondrial function contribute to depressed contractility and progressive myocardial dysfunction. CCM, delivered during the absolute refractory period, favorably modulates these pathways, restoring calcium cycling and myocardial energetics and thereby improving contractile function without increasing myocardial oxygen demand.[17] This mechanistic profile, targeting intrinsic myocyte contractile performance rather than electrical synchrony, explains both the functional gains observed across trials and the structural improvements that extend beyond what ejection fraction alone would suggest.

The observed outcome pattern can be explained by baseline characteristics and study design. Among the included trials, the study by Kadish et al.[10] contributed the largest proportion of patients and therefore exerted substantial influence on pooled estimates. Follow-up duration varied widely across studies, with some trials having relatively short observation periods —particularly relevant for clinical endpoints such as mortality and rehospitalization, as myocardial recovery and its translation into improved survival are time-dependent processes that may not be captured within limited follow-up.

Approximately forty percent of the study population had non-ischemic cardiomyopathy, an important determinant of response to CCM. Long-term observational data indicate that patients with non-ischemic cardiomyopathy experience greater and more sustained improvement in systolic function compared with those with ischemic cardiomyopathy, despite similar baseline ejection fraction, a difference that is biologically plausible and likely reflecting a lower burden of irreversible myocardial scar and a greater proportion of reversible interstitial fibrosis. Although etiology-based subgroup analyses in the present meta-analysis did not reach statistical significance, limited follow-up duration and variability across studies are the more plausible explanations.[15]

Differences in QRS stratification further contributed to heterogeneity, particularly in comparisons between CCM and CRT. Some studies, such as Zhang et al.[9], categorized patients into multiple QRS-duration groups, whereas others, such as Yuecel et al.[6], used a single cutoff around 130 ms. These differences are clinically relevant because CRT efficacy is highly dependent on QRS duration and morphology, whereas CCM acts independently of electrical synchrony, meaning the two therapies target fundamentally different pathophysiological substrates, a distinction that must be considered when interpreting comparative outcomes.

Emerging evidence suggests that the therapeutic effects of CCM may extend beyond traditional HFrEF populations. Abraham et al.[8] demonstrated that patients with ejection fraction ≥35% derived greater benefit from CCM across exercise capacity, quality of life, and NYHA functional class. These observations have prompted the ongoing AIM

HIGHer trial, which is evaluating CCM in patients with ejection fraction between 40% and 60% — a population with limited device-based treatment options, and its results will be important in defining the future scope of CCM therapy.

Finally, safety considerations are critical when interpreting the neutral findings on clinical endpoints. Despite concerns that CCM might provoke ventricular arrhythmias, available evidence does not support an increased arrhythmic risk. Studies assessing autonomic function have demonstrated reductions in sympathetic activity following CCM therapy, and ambulatory monitoring has consistently shown similar arrhythmic burden between CCM-treated patients and controls. These findings support the electrophysiological safety of CCM and suggest that the lack of observed mortality benefit is more likely related to patient selection and follow-up duration rather than adverse effects of the therapy itself.[20]

It should be noted that this is the first meta-analysis to directly compare CCM not only with OMT but also with CRT. Included studies were generally of good quality and allowed subgroup insights towards ejection fraction strata, ischemic vs non-ischemic cardiomyopathy, and QRS duration. Nevertheless, several limitations warrant consideration. The included cohort studies enrolled populations that were predominantly male (comprising up to 70-80% of participants) and with a mean age of approximately 65 years, limiting generalizability to women and younger patients. Patients with permanent Atrial Fibrillation (AF) were largely excluded due to early device requirements for P-wave sensing, despite AF being highly prevalent in heart failure, a restriction that meaningfully narrows the applicability of these findings to real-world populations. Follow-up durations were also relatively short across most studies, which may have been insufficient to capture the full extent of myocardial recovery and its downstream effects on survival. Finally, most included studies were conducted prior to the widespread adoption of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors, meaning the incremental benefit of CCM within the context of contemporary guideline-directed medical therapy may be underestimated.

Conclusion

In conclusion, this meta-analysis demonstrates the safety and efficacy of CCM as a device therapy that reliably improves symptoms, exercise capacity, and quality of life in patients with heart failure. CCM provides structural and functional benefits comparable to CRT, despite acting through a fundamentally different mechanism, and offers a meaningful therapeutic alternative for patients ineligible for resynchronization therapy, particularly those with narrow QRS duration, mildly reduced or even preserved ejection fraction. While no significant reduction in mortality or rehospitalization was observed, this likely reflects study design limitations, patient selection, and insufficient follow-up rather than an absence of clinical effect. CCM should therefore be viewed as a complementary, not competing, therapy to CRT, one that fills an important treatment gap by targeting impaired myocardial contractility rather than electrical dyssynchrony. Larger, longer, and more contemporary trials incorporating current guideline-directed medical therapy are needed to fully establish CCM's role in the modern heart failure treatment landscape.

List of Abbreviations

6MWD	6-Minute Walk Distance
AF	Atrial Fibrillation
CCM	Cardiac Contractility Modulation
CI	Confidence Intervals
CRT	Cardiac Resynchronization Therapy
HFrEF	Heart Failure with reduced Ejection Fraction
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
MD	Mean Differences
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NOS	Newcastle Ottawa Scale
NYHA	New-York Heart Association
OMT	Optimal Medical Therapy
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trials
SGLT2	Sodium-Glucose Cotransporter-2

Ethical Clearance

Not applicable.

Publication Approval

All authors are consent to the publication of this manuscript.

Author Contributions

All authors have made a significant intellectual contribution to the manuscript according to the criteria formulated by the International Committee of Medical Journal Editors

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Conflict of Interest

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Availability of Data and Materials

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Generative AI and AI-Assisted Technologies in the Writing Process

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Review Article

Bridging HFpEF Across the Care Continuum: From Screening to Phenotyping and Targeted Management

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Abstract

Heart Failure with preserved Ejection Fraction (HFpEF) has become an important form of Heart Failure (HF), characterized by marked heterogeneity in pathophysiology, clinical presentation, and treatment response. It is an increasingly prevalent form of HF driven by aging populations and comorbidities such as hypertension, diabetes, obesity, and Chronic Kidney Disease (CKD). HFpEF is also associated with high morbidity, frequent hospitalizations, and diagnostic challenges, particularly in resource-limited settings. This manuscript provides a clinically focused overview of HFpEF, integrating current concepts in pathophysiology, diagnosis, phenotyping, and management. Its pathophysiology is multifactorial, involving systemic inflammation, endothelial dysfunction, myocardial stiffness, and contributions from comorbid conditions. Emerging evidence highlights the roles of adiposity and inflammatory pathways, reinforcing the view of HFpEF as a multisystem disorder rather than purely a cardiac condition. The condition is also markedly heterogeneous, with several phenotypes identified, including cardiometabolic, obesity-related, cardiorenal, chronotropic incompetence, and Atrial Fibrillation (AF)–associated HFpEF. These phenotypes influence disease progression and therapeutic response. Additionally, numerous clinical mimics, such as pulmonary disease, valvular heart disease, and infiltrative cardiomyopathies, complicate diagnosis. Diagnosis requires a structured, probability-based approach combining clinical assessment, biomarkers, echocardiography, and, when necessary, stress testing or invasive hemodynamics. However, limited access to advanced diagnostics necessitates pragmatic, tiered approaches, especially in low-resource settings. Management focuses on three pillars: optimization of comorbidities, guideline-directed medical therapy, and phenotype-specific treatment strategies. While no therapy conclusively reduces mortality, recent advances have improved symptom control and hospitalizations. Overall, HFpEF demands a holistic, individualized approach integrating pathophysiology, clinical phenotyping, and healthcare system constraints to improve patient outcomes.

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Keywords: Heart failure, heart failure with preserved ejection fraction, echocardiography, phenotype guided management, comorbidities, guideline-directed medical therapy.

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Introduction

Heart Failure with preserved Ejection Fraction (HFpEF) has emerged as the predominant phenotype of Heart Failure (HF), representing close to half of all cases reported in most modern registries.[1] The number of individuals affected by HFpEF continues to expand globally, largely reflecting an aging population and the increasing prevalence of commonly associated comorbidities, including hypertension, Type 2 Diabetes Mellitus (T2DM), obesity, and Chronic Kidney Disease (CKD).[2-4] Despite modestly better survival rates versus those of Heart Failure with reduced Ejection Fraction (HFrEF), HFpEF continues to be associated with high rates of hospitalization and persistent symptom burden.[2-4]

A nationwide survey involving 160 cardiologists and internists practicing in Indonesia highlighted clear challenges in daily clinical practice of managing HFpEF, with 79% of respondents finding of more complex than that of HFrEF, mainly due to diagnostic ambiguity and limited access to advanced diagnostic tools.[5] There was also significant under-utilization of therapies such as Angiotensin Receptor Neprilysin Inhibitors (ARNI) and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, despite robust evidence in their prognostic benefits. These findings highlight the urgent need for a simplified, resource-adapted diagnostic and therapeutic framework that can be applied across the Indonesian healthcare system.

Our review aims to consolidate current evidence surrounding the pathophysiological processes and management of HFpEF, while proposing practical, tier-based diagnostic, phenotyping, and treatment algorithms suited to Indonesia's healthcare structure. This initiative seeks to bridge the gap between global recommendations and pragmatic implementation to improve outcomes in HFpEF care.

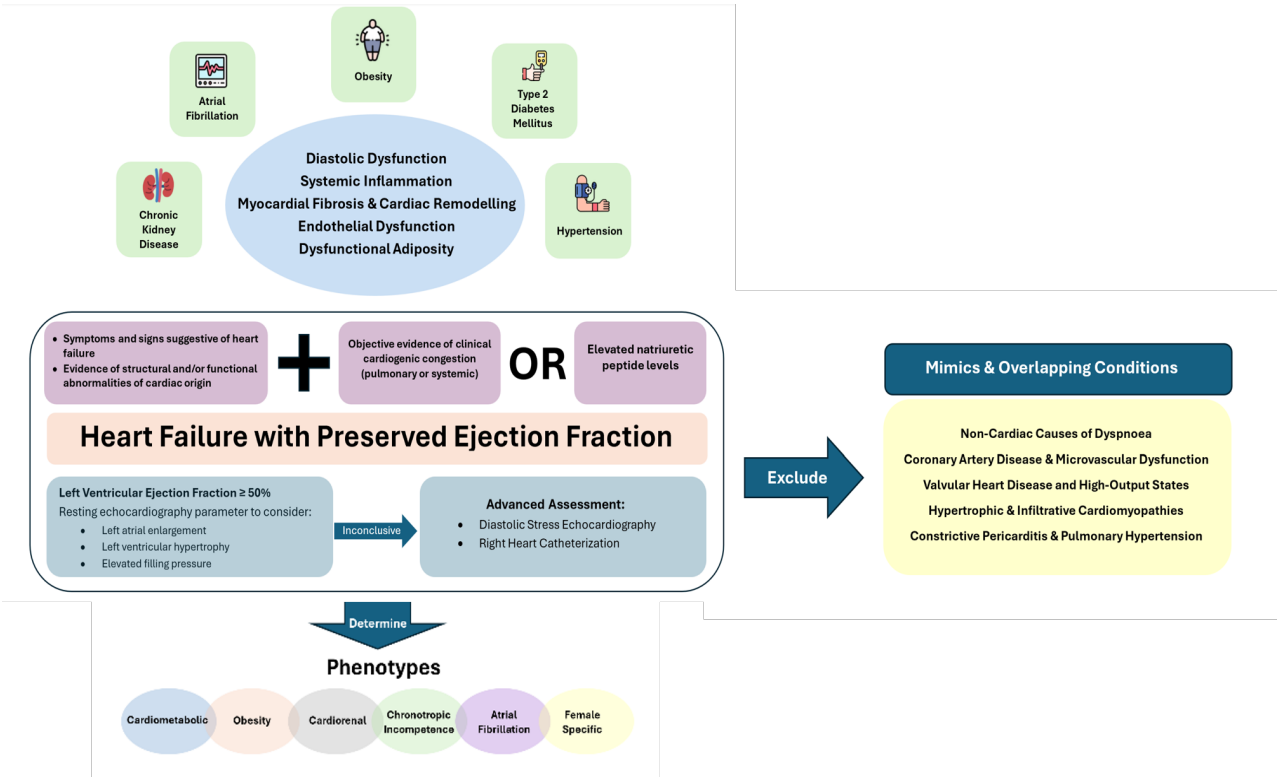

Figure 1. Integrated Diagnostic and Phenotyping Framework for Heart Failure with Preserved Ejection Fraction (HFpEF). Common cardiometabolic comorbidities (obesity, type 2 diabetes mellitus, hypertension, chronic kidney disease, and atrial fibrillation) drive a shared pathophysiological substrate characterized by systemic inflammation, myocardial fibrosis and remodeling, endothelial dysfunction, and diastolic impairment. HFpEF diagnosis requires symptoms and/or signs of heart failure, preserved left ventricular ejection fraction (≥50%), objective structural or functional cardiac abnormalities, and either elevated natriuretic peptide levels or evidence of congestion. Resting echocardiography (e.g., left atrial enlargement, left ventricular hypertrophy, elevated filling pressures) is central, with advanced testing (diastolic stress echocardiography or right heart catheterization) recommended when inconclusive. Mimics and overlapping conditions must be excluded. Following diagnosis, patients are stratified into clinical phenotypes (e.g., cardiometabolic, obesity-related, cardiorenal, chronotropic incompetence, atrial fibrillation-related, and female-specific) to guide targeted management.

Discussion

Pathophysiology of HFpEF – Comorbidities, Inflammation & Adiposity

Alongside the 'Universal Definition of Heart Failure', HFpEF is further defined as HF with a Left Ventricular Ejection Fraction (LVEF) of 50% or more, accompanied by objective evidence of cardiac structural and/or functional abnormalities consistent with diastolic dysfunction and elevated Left Ventricular (LV) filling pressures.[2-4,6-9] These abnormalities may include any combination of left atrial enlargement, LV hypertrophy, abnormal diastolic indices on Transthoracic Echocardiography (TTE), or elevated circulating Natriuretic Peptides (NP) (Figure 1).

Early conceptual models emphasized abnormalities in LV relaxation and increased myocardial stiffness following long-standing comorbidities such as hypertension as a principal mechanism responsible for diastolic dysfunction, elevated LV End-Diastolic Pressure (LVEDP), and subsequent development of HF.[3-4,6] However, subsequent research has demonstrated that HFpEF arises from a broader multi-systemic process, including that of physiological aging and pathological cardiometabolic comorbidities. Furthermore, although diastolic dysfunction is a recognized clinical feature in HFpEF, there is evidence that echocardiographic features commonly used to define and grade diastolic dysfunction may not be present in most cases of HFpEF, as confirmed by invasive hemodynamics.[10] This further supports the rather complex, multifactorial pathophysiology underlying HFpEF (Figure 1).

A landmark paradigm proposed that common comorbidities such as hypertension, obesity, T2DM, and CKD promote systemic inflammation and coronary microvascular endothelial dysfunction, involving inhibition of the cyclic guanosine monophosphate-protein kinase G signaling pathway and resulting in myocardial stiffness and fibrosis.[11-12] Beyond intrinsic myocardial abnormalities, coronary microvasculature, and peripheral endothelial dysfunction commonly co-exist as well. Increased arterial stiffness and enhanced wave reflections augment LV afterload and diminish diastolic suction, further increasing LV wall stress and contributing to pulmonary venous congestion, particularly during exertion. Skeletal muscle dysfunction (linked to reduced capillary density, mitochondrial abnormalities, and impaired oxygen utilization) often adds insult to injury.[3-4,11-12] Increasing attention has also focused on the contribution of atrial myopathy and Atrial Fibrillation (AF) to HFpEF pathophysiology, by eliminating atrial contraction, exacerbating ventricular filling abnormalities, creating a vicious cycle that accelerates disease progression.[13]

Recently, adiposity has been implicated in the development of HFpEF.[14-16] The adipokine-mediated hypothesis centers around visceral adiposity, and it describes the secretion of pro-inflammatory, pro-hypertrophic, and pro-fibrotic adipokines from visceral fat depots. Adipokines act as the molecular mediators for systemic inflammation, myocardial hypertrophy, myocardial fibrosis, and microcirculatory dysfunction.[14-16] An interesting proposition includes the idea that distribution, as opposed to absolute amount or mass, of adiposity may be a more important factor in the pathogenesis of the condition.

This multidimensional pathophysiology explains the marked heterogeneity observed among patients and has led to the recognition of several HFpEF phenotypes, each associated with distinct clinical trajectories and therapeutic responses.[14] Understanding this integrative model helps explain why traditional HF therapies that target only cardiac hemodynamics have shown limited benefit and underscores the need for phenotype-directed treatment strategies that address the broader systemic mechanisms underlying HFpEF. Clinical phenotyping provides a mechanistic framework to stratify patients based on dominant drivers of myocardial dysfunction, systemic comorbidity burden, and hemodynamic patterns. Such classification is not merely descriptive – it has implications for prognosis and therapeutic responsiveness.

Phenotypes, Mimics & Overlapping Conditions in Patients Living with HFpEF (Figure 1)

Cardiometabolic Phenotype

The cardiometabolic phenotype is the most prevalent HFpEF subtype and is characterized by hypertension, T2DM, visceral adiposity, and Metabolically Associated Fatty Liver Disease (MAFLD). An associated inflammatory–microvascular axis leads to concentric remodeling, extracellular matrix expansion, and impaired ventricular–vascular coupling. Hypertension, in particular, plays a central mechanistic role in the

cardiometabolic HFpEF phenotype by promoting arterial stiffening, increased wave reflections, and augmented pulsatile afterload, all of which impair ventricular–vascular coupling and delay myocardial relaxation.[11] In the cardiometabolic phenotype, Renin-Angiotensin-Aldosterone System (RAAS) activation represents a biologically coherent downstream consequence of obesity, insulin resistance, and hypertension rather than an isolated neurohormonal event.[13,15-16] Aldosterone-mediated mineralocorticoid receptor activation promotes myocardial fibroblast proliferation, collagen deposition, extracellular matrix expansion, and microvascular inflammation, directly contributing to ventricular stiffening and impaired diastolic compliance. Mineralocorticoid receptor signaling also amplifies inflammatory pathways central to the cardiometabolic HFpEF paradigm.[17] These mechanistic links provide biological plausibility for RAAS and mineralocorticoid receptor antagonism in this phenotype, and would support the results from pivotal clinical trials such as FINEARTS-HF.[18]

MAFLD, an increasingly recognized comorbidity associated with HFpEF, has been independently associated with subclinical myocardial remodeling and impaired diastolic function, even in asymptomatic individuals. Implicated pathophysiological processes linked to the bidirectional relationship between MAFLD and HFpEF, aside from hepatic congestion, portal hypertension, and cirrhosis, include the presence of systemic inflammation, oxidative stress, insulin resistance, RAAS activation, and atherosclerosis.[19] Thus, several proposed therapeutic nodes have been suggested as potential treatment options, pending clinical trials, including existing drug classes such as RAAS and SGLT2 inhibition, as well as more novel therapeutics involving IL-1/IL-6 inhibition and glucagon-like peptide-1 receptor agonists.[19]

Obesity Phenotype

Obesity functions not merely as a comorbidity but as a pathophysiological amplifier in HFpEF. Adiposity promotes systemic inflammation through adipokine secretion and oxidative stress, leading to endothelial dysfunction and myocardial fibrosis.[16-17,20-22] Epicardial adipose tissue exerts local paracrine effects that impair myocardial relaxation and promote extracellular matrix deposition. Obesity also induces plasma volume expansion and increased preload, resulting in exaggerated rises in filling pressures during exertion. Reduced circulating NP levels in obese individuals, attributed to enhanced neprilysin activity and increased clearance, may mask congestion and delay diagnosis.[17,20-22] Lower NP levels are also associated with enhanced aldosterone signaling, perpetuating sodium retention and ventricular stiffness.[22]

Cardiorenal Phenotype

Renal dysfunction is highly prevalent in HFpEF and represents a central component of disease heterogeneity. CKD contributes not only to sodium retention and volume expansion but also to systemic inflammation, endothelial dysfunction, vascular calcification, and neurohormonal activation. The cardiorenal phenotype is therefore increasingly recognized as a multispecialty disorder involving complex bidirectional heart–kidney interactions.[23-24] Reduced glomerular filtration rate promotes plasma volume expansion and elevated LV filling pressures. Beyond hemodynamic congestion, renal impairment is strongly associated with adverse cardiovascular outcomes, including increased mortality and hospitalization risk in patients with HF.[23-25] Uremic toxins, oxidative stress, and chronic inflammation stimulate fibroblast activation and extracellular matrix deposition, leading to myocardial fibrosis and increased passive stiffness. RAAS activation and sympathetic overactivity further amplify ventricular–vascular uncoupling and arterial stiffening.[23-25] Elevated central venous pressure further impairs renal perfusion, perpetuating a vicious cycle of congestion and renal dysfunction.[23-25]

Chronotropic Incompetence & Exercise Intolerance Phenotype

Chronotropic incompetence and exercise intolerance are frequently observed in HFpEF.[25-27] Pandey et al. demonstrated that reduced heart rate augmentation and exaggerated increases in Pulmonary Capillary Wedge Pressure (PCWP) were strongly associated with reduced Peak Oxygen Consumption (VO_2 max) in HFpEF.[27] Impaired heart rate augmentation limits cardiac output reserve and contributes substantially to exertional intolerance in HFpEF. There is also growing interest in heart rate modulation in managing HFpEF, where clinical trials center around Beta-Blockers (BB) and rate-limiting pharmacotherapy withdrawal, as well as rate-adaptive pacing have been designed in selected phenotypes of HFpEF, to test the theory of personalized heart rate modulation.[28] However, exercise limitation is not solely cardiac in origin. Sarma et al. demonstrated that patients with HFpEF had lower VO_2 max and exercise heart rate than older controls, but sinus node dysfunction could not be entirely attributed to chronotropic incompetence.[26] Initially thought to be mainly driven by impaired

chronotropic reserve and rhythmic disturbances, the phenomenon is now increasingly understood to involve multi-system contributors, including pulmonary vascular remodeling, lung disease, adiposity, renal dysfunction, peripheral factors, and myocardial remodeling.[29] At the tissue level, peripheral abnormalities, including skeletal muscle mitochondrial dysfunction, reduced capillary density, impaired oxidative metabolism, and diminished oxygen extraction, have been shown to contribute to restricted aerobic capacity in HFpEF.[27, 29]

Atrial Fibrillation Phenotype

AF can often mimic HFpEF when suboptimally managed.[13] Furthermore, loss of atrial contraction, irregular ventricular filling, and altered NP levels complicate the interpretation of both clinical symptoms and investigation findings. In such cases, clinicians should maintain a low threshold in performing advanced imaging or invasive hemodynamic monitoring when diagnostic uncertainty persists.[13,30-31] Left atrial dysfunction itself, however, has also emerged as a key mechanistic and prognostic substrate in HFpEF.[30-31] Atrial cardiomyopathy is defined as structural or functional atrial abnormalities independent of arrhythmia burden, and it may develop as a consequence of elevated filling pressures or exist as a primary substrate. AF has been shown to be both a consequence and a driver of atrial cardiomyopathy and HFpEF progression, in which elevated LV filling pressures lead to progressive left atrial remodeling, fibrosis, and loss of compliance, resulting in impaired reservoir, conduit, and booster-pump function and a predisposition to AF. AF, in itself, induces metabolic and structural remodeling, resulting in poor atrial compliance. More importantly, the co-existence of AF and HFpEF accelerates pulmonary hypertension development and worsens prognosis, and management of concomitant disease remains complex.[30-32]

Special Consideration in Female Patients with HFpEF

A distinct and clinically relevant HFpEF phenotype is the female-predominant cardiometabolic–inflammatory phenotype, typically observed in post-menopausal women.[33-34] This phenotype is characterized by a high burden of obesity, hypertension, and metabolic dysfunction, with a strong interplay between visceral adiposity, systemic inflammation, and Microvascular Dysfunction (MVD). Loss of oestrogen plays a central mechanistic role, leading to endothelial dysfunction, impaired nitric oxide bioavailability, and activation of pro-inflammatory and neurohormonal pathways, including the renin–angiotensin–aldosterone system.[33-34] This results in increased vascular stiffness, concentric remodeling, and diastolic dysfunction. In parallel, adipose tissue–driven inflammation promotes cytokine activation (e.g., IL-6, TNF-α), oxidative stress, and coronary MVD, further impairing myocardial relaxation.[33-34] Clinically, women exhibit smaller ventricular cavities, higher LV stiffness, and greater impairment in diastolic reserve during exercise, contributing to exertional intolerance despite preserved LVEF.[33-34] This phenotype underscores that HFpEF in women represents a distinct biological entity, driven by sex-specific hormonal, metabolic, and inflammatory mechanisms.

Clinical Mimics in HFpEF (Figure 1)

Non-Cardiac Causes of Dyspnoea

There are various causes of dyspnoea, beyond that of HFpEF. Anemia, Chronic Obstructive Pulmonary Disease (COPD), obstructive sleep apnoea, and thyroid disorders are particularly important mimics as they independently contribute to dyspnoea and other overlapping symptoms, but also remain highly prevalent in HFpEF populations.[14, 35-36] In the case of COPD, it frequently coexists with HFpEF due to shared risk factors. Systemic inflammation and chronic hypoxia promote pulmonary vasoconstriction and right ventricular remodeling. Lung hyperinflation alters ventricular interdependence and impairs diastolic filling, leading to complex hemodynamic interactions that worsen clinical outcomes.[35-36] Targeted treatment of these abnormalities may significantly improve symptoms, regardless of co-existing HFpEF.[14] Therefore, HFpEF should not be diagnosed solely on the basis of symptoms when alternative systemic causes are plausible. When available, cardiopulmonary exercise testing or exercise echocardiography provides additional discriminatory value by distinguishing ventilatory limitation from circulatory impairment, particularly in diagnostically uncertain cases, although accessibility may be an issue, especially in resource-limited settings.[37]

Coronary Artery Disease & Coronary Microvascular Dysfunction

Coronary Artery Disease (CAD) is more prevalent in patients with HFpEF and is independently associated with worse clinical outcomes. Observational analyses have demonstrated that the presence of CAD correlates with greater structural remodeling, higher filling pressures, and increased rates of hospitalization and mortality.[38-39] Evaluation

for ischemic heart disease should be undertaken in patients with suggestive clinical features, including typical angina, high-risk cardiovascular profiles, electrocardiographic abnormalities, or regional wall motion abnormalities on cardiac imaging. Various forms of non-invasive diagnostic tests, including exercise stress testing, stress echocardiography, nuclear-based stress imaging, or coronary computed tomography angiography, may be used depending on patient characteristics and local expertise. Recognition is clinically important, as targeted anti-ischemic therapy or revascularization may alleviate symptoms and improve outcomes when ischemia coexists with HFpEF.[39-41]

Coronary MVD further contributes by impairing subendocardial perfusion and promoting myocardial fibrosis and diastolic dysfunction.[41-42] An important aspect to appreciate includes the high prevalence of MVD among patients affected by HFpEF, which can occur despite normal or mildly diseased epicardial coronary arteries. Guidelines recommend either non-invasive (i.e., positron emission tomography or cardiac MRI to assess myocardial perfusion and flow reserve) and/or invasive testing (i.e., cardiac catheterization measurements of coronary flow reserve and index of microvascular resistance) for coronary MVD, although availability of facilities and expertise remains sparse in our region.[40-42]

Valvular Heart Disease and High-Output States

Valvular heart disease, particularly aortic stenosis and mitral regurgitation, frequently results in congestion with preserved LVEF and may be misclassified as HFpEF if echocardiographic assessment is not performed comprehensively. Both the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines emphasize TTE as the cornerstone for identifying valvular pathology and determining whether symptoms are primarily valve-mediated or attributable to HFpEF physiology.[6,8,43] Similarly, high-output states, including severe anemia, thyrotoxicosis, and arteriovenous shunts, can present similarly with clinical congestion, despite preserved systolic function. Identification of these conditions is essential because management strategies differ fundamentally from standard HFpEF-directed therapy.

Hypertrophic & Infiltrative Cardiomyopathies

Hypertrophic Cardiomyopathy (HCM) is a well-recognized HFpEF mimic, presenting with exertional dyspnoea, preserved LVEF, and diastolic dysfunction.[45] Distinguishing features include asymmetric or disproportionate LV hypertrophy, dynamic LV outflow tract obstruction, characteristic electrocardiographic abnormalities, family history of cardiomyopathy or sudden cardiac death, and specific patterns of late gadolinium enhancement on Cardiac Magnetic Resonance (CMR) imaging.[45] Misclassification of HCM as HFpEF may delay disease-specific therapies and appropriate family screening.[44-45] In elderly patients, differentiation from hypertensive heart disease may be challenging, and clinicians should carefully assess "red flags," including marked wall thickness, discordant electrocardiogram voltage, unexplained hypertrophy, and history of syncope.[45-46]

Infiltrative cardiomyopathies, particularly cardiac amyloidosis, are increasingly recognized among patients initially labeled as HFpEF and represent an important diagnostic consideration, especially in older individuals with increased wall thickness.[45-46] Transthyretin Cardiac Amyloidosis (ATTR-CM) is increasingly identified in patients previously diagnosed with HFpEF, and accurate diagnosis is critical given the availability of disease-modifying therapies. Clinical and extracardiac "red flags" that may raise suspicion include carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, peripheral neuropathy, and intolerance to conventional HF therapies.[45-46] Imaging findings suggestive of amyloidosis include increased ventricular wall thickness with bi-atrial enlargement, restrictive filling patterns, discordance between low QRS voltage and wall thickness, apical sparing on strain imaging, and characteristic CMR features.[46] Bone tracer scintigraphy enables non-invasive diagnosis of ATTR-CM in the absence of monoclonal protein, thereby reducing the need for endomyocardial biopsy in appropriate cases.[46]

Constrictive Pericarditis & Pulmonary Hypertension

Constrictive pericarditis is a classic mimic of HFpEF, characterized by preserved ejection fraction with symptoms of congestion due to pericardial constraint rather than intrinsic myocardial dysfunction.[47] Key diagnostic features include respiratory variation in Doppler inflow velocities, annulus reversus or paradoxus, pericardial thickening or calcification on computed tomography or CMR imaging, and confirmatory invasive hemodynamic findings when non-invasive evaluation is inconclusive.[47]

Pulmonary hypertension (PH) frequently coexists with HFpEF but may also represent a primary pulmonary vascular disorder.[48] Accurate

classification requires careful measurement and interpretation of PCWP, as misclassification may lead to inappropriate treatment, including the use of pulmonary vasodilators in patients with left heart disease. When available, exercise hemodynamic assessment can reveal exertional elevation in filling pressures, thereby identifying 'masked' HFpEF and distinguishing it from primary pulmonary arterial hypertension.[49-50] This differentiation is clinically crucial, as therapeutic strategies differ substantially between these conditions.

Diagnostic Approach to Heart Failure with Preserved Ejection Fraction

Conceptual Framework for Diagnosis

The diagnostic pathway for HFpEF should be probability-based and stepwise, integrating symptoms and signs with objective evidence of cardiac dysfunction or congestion. Contemporary guidance emphasizes that HF is a clinical syndrome supported by biomarkers and/or objective findings, and that HFpEF requires demonstration of

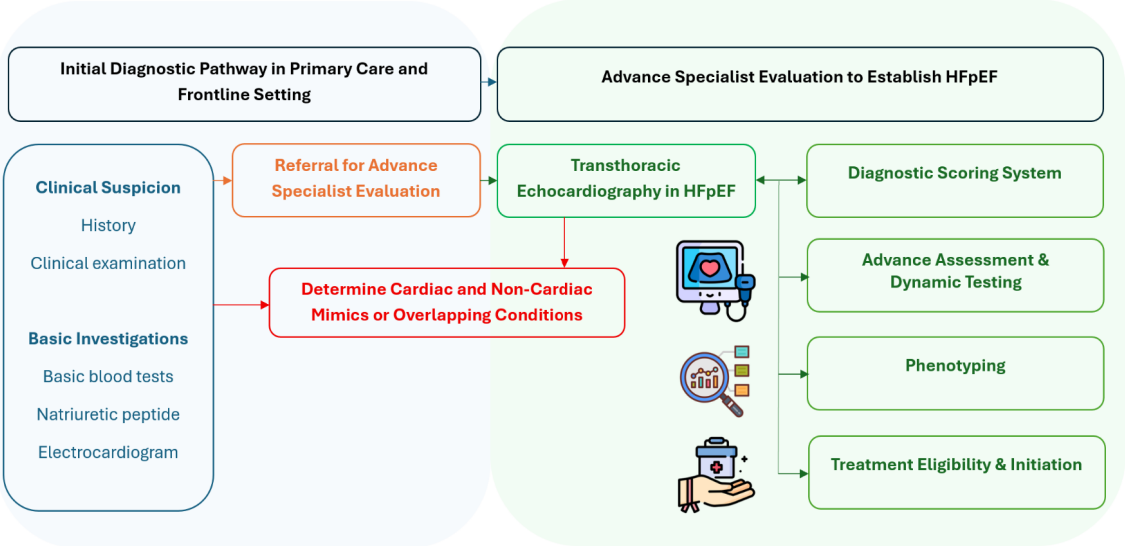

Figure 2. Stepwise Diagnostic Pathway for HFpEF from Primary Care to Specialist Evaluation. In primary care, HFpEF is suspected based on clinical assessment and basic investigations (blood tests, natriuretic peptides, ECG), prompting referral. Specialist evaluation centers on transthoracic echocardiography and exclusion of cardiac and non-cardiac mimics. Diagnosis is supported by scoring systems and advanced testing when needed. Confirmed HFpEF is followed by phenotyping and initiation of targeted therapy.

preserved LVEF together with evidence consistent with elevated filling pressures, either at rest or during physiological stress.[6,50] Because many patients with HFpEF have near-normal resting hemodynamics, contemporary diagnostic strategies increasingly incorporate dynamic functional testing to reveal abnormal reserve and exertional rises in filling pressure.[6,49-52]

The workflow is therefore structured according to tiers of care:

- Primary care and frontline clinicians aim to identify suspected HF and refer patients suspicious of HFpEF, and
- Subspecialists, commonly cardiologists, aim to confirm the diagnosis of HFpEF using TTE and diagnostic scores, and/or perform further investigations to support the clinical suspicion.

Initial Diagnostic Pathway in Primary Care and Frontline Setting (Figure 2)

Clinical suspicion typically arises when patients present with symptoms associated with HF, commonly exertional dyspnoea, reduced exercise tolerance, fatigue, orthopnoea or paroxysmal nocturnal dyspnoea, or peripheral edema.[2-4,6,50] Furthermore, from clinical history, suspicion is heightened further based on the context of having risk factors commonly associated with HFpEF, such as older age, hypertension, obesity, T2DM, CKD, and AF. This is corroborated by clinical examination findings such as an elevated jugular venous pressure, pulmonary crackles, or peripheral edema, although such findings may be absent in early or latent HFpEF.[2-4,6,50]

From here, clinicians should then embark on basic clinical investigations with TWO goals in

mind – to support the possibility of a cardiac etiology, alongside identifying potential alternative diagnoses for the clinical presentation.[2-4,6,50] Routine blood investigations should include a full blood count, renal function and electrolytes, liver function test, glucose or glycated hemoglobin, and thyroid function test to help identify potential mimics such as anemia or thyroid disease, assess comorbidity burden, and provide baseline values for subsequent management. Electrocardiography may reveal AF, LV hypertrophy, past myocardial infarctions, or conduction disease. However, a normal electrocardiogram does not eliminate the likelihood of HF. Chest radiography can demonstrate cardiomegaly, pulmonary congestion, pleural effusion, or alternative pulmonary pathology.

NP levels, however, remain the most useful triage investigation in HF. Cut-off values for NP depend on the clinical setting (i.e., ambulatory outpatient clinics versus emergency department) and age.[53] Other clinical considerations include the presence or absence of obesity, AF, and renal dysfunction, although cut-off values in these settings are yet to be formally established.[53] In addition, it is known that HFpEF can exist even in the absence of elevated NP levels.[54-55] Thus, in patients highly suspicious of the condition, a referral for further investigations is still warranted, regardless of NP levels.

Although scoring systems to determine the probability of HFpEF would prove to be useful in the community setting as a triage tool, two of the most commonly used scoring tools (i.e., H2FPEF and HFA-PEFF) include parameters requiring TTE, which often remain poorly accessible to most clinicians.[50,56] An alternative tool to help with referral decisions includes the HFpEF-ABA scoring system, derived from the H2FPEF scoring tool, which utilizes only THREE parameters – age, body mass index, and AF, which can easily be determined in the community setting.[57] The HFpEF-ABA score largely demonstrated reasonably strong discrimination and calibration across ambulatory patients with dyspnoea, although validation studies across various populations, including Indonesia, remain limited.

Table 1. Echocardiographic criteria for estimating elevated left ventricular filling pressure in sinus rhythm and atrial fibrillation.

A. Echocardiographic Criteria for Estimating Elevated Left Ventricular Filling Pressure in Sinus Rhythm.				
Mitral E/A ratio ≥2 (as a single strong indicator of elevated filling pressure) OR Mitral E/A ratio between 0.8 and 2.0, in conjunction with at least two of the following: • LAVI >34 mL/m² • TR velocity ≥2.8 m/s or PASP ≥35 mmHg • E/e' ratio ≥15 (septal), ≥13 (lateral), or ≥14 (average) • LASr ≤16% • LV mass index >95 g/m² in women or >115 g/m² in men				
B. Echocardiographic Criteria for Estimating Elevated Left Ventricular Filling Pressure in Atrial Fibrillation.				
Elevated LVFP is suggested when at least three of the following are present: • mitral E velocity ≥100 cm/s • septal E/e' >11 • TR velocity >2.8 m/s or PASP >35 mmHg • deceleration time ≤160 ms				
In the absence of definitive parameters, additional supportive indices may include:				
PR end-diastolic velocity ≥2 m/s	pulmonary artery diastolic pressure ≥16 mmHg	mitral inflow L-wave velocity ≥50 cm/s	Ar–A duration >30 ms*	and/or a decrease in mitral E/A ratio ≥50% with Valsalva manoeuvre*

This table summarizes key echocardiographic parameters used to estimate elevated left ventricular filling pressure (LVFP) in patients with preserved ejection fraction who are in sinus rhythm or atrial fibrillation (AF). In AF, conventional diastolic parameters are less reliable due to beat-to-beat variability and absence of atrial contraction, thus the need for unique parameters. Peak early diastolic mitral inflow velocity (E), peak atrial contraction mitral inflow velocity (A), left atrial volume index (LAVI), tricuspid regurgitation (TR), pulmonary artery systolic pressure (PASP), peak early diastolic mitral annular tissue velocity (e'), left atrial reservoir strain (LASr), left ventricle (LV), pulmonary regurgitation (PR), and pulmonary vein atrial reversal wave to the mitral late diastolic atrial flow wave duration ratio (Ar–A).

Advance Specialist Evaluation to Establish HFpEF (Figure 2)

Upon referral for advanced evaluation, further assessment often begins by performing a TTE, and the utilization of scoring systems to determine the probability of having HFpEF. In certain circumstances, additional investigations (both invasive and non-invasive) may be required depending on clinical context, expertise, and availability.

Transthoracic Echocardiography in HFpEF (Table 1 & Supplementary Table 1)

TTE remains the cornerstone imaging modality in the diagnostic evaluation of HFpEF, providing essential information for confirmation of cardiac involvement, assessment of hemodynamic burden, exclusion of alternative diagnoses, and prognostication.[50,58-59] Furthermore, given the non-specific clinical presentation of HFpEF, TTE is indispensable for differentiating HFpEF from a broad range of cardiac and non-cardiac conditions that may mimic the condition, while also offering insight into the underlying pathophysiological mechanisms driving the syndrome.[50,58-59]

HFpEF is commonly associated with characteristic remodeling of the LV. Structural abnormalities frequently observed include LV hypertrophy, specifically that of concentric remodeling (assessed using LV mass index and relative wall thickness) and left atrial enlargement (assessed using Left Atrial Volume Indexed [LAVI]). In addition, assessment for elevated filling pressure is routinely performed and largely reflects a combination of impaired relaxation, reduced contractile reserve, abnormal atrioventricular coupling, increased ventricular stiffness, relative pericardial restraint, and abnormal ventricular-vascular coupling (Table 1).[50,58-59] It should be remembered that a multiparametric approach rather than reliance on any single variable is often advised when assessing diastolic function.

In AF, assessment for diastolic function may still be performed, although it may be more challenging (Table 1).[58-59] In such cases, elevated filling pressure is suspected when several supportive features are present, including increased mitral E velocity, increased septal E/e', shortened deceleration time, and increased tricuspid regurgitation velocity or pulmonary artery systolic pressure. In addition, these algorithms should not be applied uncritically in certain settings, including left bundle branch block, right ventricular pacing or cardiac resynchronization therapy, severe mitral valve disease or prosthetic mitral valves, heart transplantation, LV assist device support, non-cardiac pulmonary hypertension, and constrictive pericarditis.[58-59] Further staging of HFpEF phenotypes based on echocardiography can also be performed, as per previous studies, with significance in prognostication.[60-61] However, classification based on such phenotypes requires further validation in its clinical utility. An example of echocardiographic-based stratification and classification is listed in Table 2.

However, as previously discussed, echocardiographic-based changes used in diastolic functional assessment may not be present in all cases of confirmed HFpEF.[10] Conversely, many individuals, particularly older adults, may exhibit echocardiographic features of diastolic dysfunction without having clinical features suggestive of HFpEF, underscoring why isolated diastolic dysfunction should not be used as a surrogate for diagnosis.[50,58-59] Contemporary concepts emphasize HFpEF as a syndrome of abnormal pressure-volume responses to physiological stress, in which resting echocardiographic findings may underestimate disease severity. Therefore, in cases of high clinical suspicion where resting TTE is revealed to be non-suggestive of the condition, assessment should move beyond measurements at resting state toward a comprehensive interpretation of cardiac structure, function, and dynamic reserve with physiological stress, which will be discussed in another section.

One of the primary roles of TTE in suspected HFpEF is the exclusion of other conditions that may mimic or overlap with HFpEF, of which may require distinct management strategies.[2-4,6,50] These include restrictive or infiltrative cardiomyopathies, HCM, ischemic heart disease, HF with improved ejection fraction, pulmonary arterial hypertension, constrictive pericarditis, valvular heart disease, high-output states, and primary pulmonary disease. Accurate identification of these entities is critical, as misclassification as HFpEF may delay disease-specific therapy and adversely affect outcomes. Furthermore, depending on clinical suspicion, additional investigations may be required outside of TTE, including ischemia evaluation, CMR imaging for infiltrative disease, invasive hemodynamic assessment for constrictive pericarditis, or targeted pulmonary evaluation.

Diagnostic Scoring Systems, Advanced Assessment & Dynamic Testing (Figure 2)

When clinical investigations performed at rest remain indefinite, validated diagnostic scores may help with the diagnosis and treatment planning in HFpEF management. TWO popular scoring systems are often used – the H2FPEF and HFA-

Table 2. Echocardiography-based staging of heart failure with preserved ejection fraction.

Stage 1: Isolated Left Ventricular Involvement
• Echocardiographic clusters, as per ASIAN-HF registry: ○ normal left ventricular (LV) structure; with elevated filling pressures ○ restrictive; small LV cavities, concentric hypertrophy, and low stroke volume ○ hypertrophic; with concentric LV hypertrophy ○ high-output; with increased stroke volume ○ atrial-dominant; driven by atrial myopathy ○ others (not clearly defined)
LV structural and functional parameters: concentric LV hypertrophy (i.e., LV mass index ≥115 g/m² in men or ≥95 g/m² in women, RWT >0.42), reduced LV compliance, elevated LV filling pressures (E/e' >9), and impaired forward flow with reduced cardiac output.
Stage 2: Left Atrial Myopathy (Isolated or Predominant)
• Left atrial (LA) dysfunction may be disproportionate to the degree of left ventricular diastolic abnormality and can act as an important driver of symptoms, pulmonary hypertension, and atrial fibrillation in HFpEF. • LA dysfunction has been linked to incident atrial fibrillation and progression to permanent arrhythmia, increased pulmonary vascular resistance and right ventricular dysfunction, contributing to worse clinical outcomes.
LA dilatation parameters: LAVI >34 mL/m² in sinus rhythm, or >40 mL/m² in atrial fibrillation LA dysfunction parameters: impaired left atrial reservoir strain (peak atrial longitudinal strain ≤ 24%), and increased left atrial stiffness or reduced atrial compliance.
Stage 3: Pulmonary Vasculature Involvement with Pulmonary Hypertension, with or without Right Atrial & Ventricular Dysfunction
• Pulmonary hypertension (PH) in HFpEF may arise passively from elevated left-sided filling pressures or evolve into a combined pre- and post-capillary process due to pulmonary vasoconstriction and vascular remodelling in chronic disease states. • Right ventricular (RV) dysfunction reflects both load-dependent and intrinsic myocardial impairment. • Right atrial (RA) myopathy is increasingly recognised as part of advanced HFpEF, and it correlates with a higher burden of atrial fibrillation, more severe pulmonary vascular disease, significant tricuspid regurgitation, RV dysfunction, and adverse prognosis.
Pulmonary vasculature abnormalities: tricuspid regurgitation peak velocity >2.8m/s, pulmonary artery systolic pressure > 35mmHg RV dysfunction: reduced RV fractional area change <35%, tricuspid annular plane systolic excursion (TAPSE) <17 mm, or tricuspid annular systolic velocity (RV S') < 9.5cm RA dilatation: RA enlargement (RA volume index >39 mL/m² in men and >33 mL/m² in women) RA dysfunction: reduced RA reservoir strain (≤19.8%),

This table describes the various stages of cardiac abnormalities, and corresponding parameters, that can potentially be observed and measured through cardiac imaging.

PEFF scores.[50-56] An earlier-mentioned scoring system, the HFpEF-ABA, is actually a derivative of the H2FPEF tool and will not be discussed further in this section.

The H2FPEF score combines clinical variables, including obesity and AF, with echocardiographic surrogates of filling pressure to estimate diagnostic likelihood and guide further investigation.[56] The HFA-PEFF algorithm integrates echocardiographic parameters and NP into major and minor criteria to stratify patients into low, intermediate, or high probability of HFpEF, recommending functional testing in intermediate-probability patients.[50]

Comparative analyses support the complementary use of these tools, where high scores have been shown to be useful to support the diagnosis of the condition, whereas intermediate scores help identify patients who would most likely benefit from further investigations, ideally those which are exercise or stress-based.[62] Furthermore, these scores have been shown to assist in functional assessment, outcome prediction, and prognostication when incorporated into daily clinical practice.[63-64]

However, there remain issues with potential misclassification, specifically when using low scores using either of the scoring tools, to confidently rule out a diagnosis of HFpEF.[62] As previously

mentioned, HFpEF is a syndrome of abnormal pressure-volume responses to physiological stress, and therefore, clinical parameters obtained at rest may severely underestimate the presence of the condition. In such cases, where a diagnostic scoring system demonstrates an intermediate probability of having the condition, it is recommended that either a non-invasive diastolic stress test or invasive hemodynamic testing be performed.

Diastolic Exercise Stress Echocardiography

When resting TTE is unremarkable or inconclusive, particularly in patients with suggestive symptoms like exertional dyspnoea, exercise stress echocardiography can be performed to unmask latent HFpEF. Exercise stress echocardiography is typically performed using a supine bicycle, with a fixed protocol reminiscent of a treadmill exercise stress test for ischemia evaluation.[65-67] However, parameters measured during the test are specific to those of diastolic function and reserve, as well as pulmonary pressure response to exercise or stress. Key parameters include mitral inflow velocities, E/e' ratio, tricuspid regurgitation velocity, and left atrial functional indices. Abnormal exercise filling pressures are suggested by either a raised E/e' and/or raised tricuspid regurgitation velocity during exercise.[65-67]

Right Heart Catheterization

Alternatively, or if stress echocardiography remains non-diagnostic or inaccessible, invasive hemodynamic testing can be considered. Invasive testing is particularly valuable in patients with obesity, AF, unexplained exertional dyspnoea, or coexisting pulmonary disease, where non-invasive indices may be less reliable.[65,67-69] Right Heart Catheterization (RHC) allows direct measurement of PCWP to help confirm a diagnosis of HFpEF, where PCWP of >15 mmHg at rest is fairly suggestive of the disease.[68-70] Some may opt for direct catheter-based measurement of LVEDP to support the diagnosis of HFpEF. However, there continues to be uncertainty with regard to which measurements (i.e., PCWP versus LVEDP) are most diagnostic for HFpEF, although the former has been shown to be a better predictor of prognosis in the condition.[71]

Similar to exercise stress echocardiography, there is added value in performing RHC with exercise, most commonly through the use of a supine bicycle. Following exercise, a PCWP of ≥25 mmHg would be suggestive of HFpEF and remains the gold standard in diagnosing the condition.[65,68-70] In the event that a supine bicycle is unavailable, various other methods have been employed in the past, including the use of passive leg raises, direct volume challenge using saline, and complex use of conductance catheterization to assess pressure-volume loops of the right ventricle and pulmonary artery, which go beyond the scope of this review.[65,68-70] There also remains contention with regard to performing RHC in either an upright or supine position, which are beyond the aims of this article.[71]

Common Pitfalls and Diagnostic Errors

One of the most common pitfalls in the diagnosis of HFpEF is over-reliance on resting echocardiographic indices, which can lead to both under- and misdiagnosis in routine clinical practice. Various cardiac conditions may exhibit similar echocardiographic features, including structural abnormalities and hemodynamic changes suggestive of diastolic dysfunction, including both hypertrophic and infiltrative cardiomyopathies, as well as valvular heart disease.[2-4,6,50] As the treatment for each of these conditions differs greatly from that of HFpEF phenotypes, it would be prudent to identify features that would help distinguish these mimics early through TTE, so as to not delay further investigations, such as cardiac MRI or nuclear imaging, that are required to diagnose these conditions, specifically cardiomyopathies such as cardiac amyloidosis.

In addition, the use of diagnostic scoring systems may not necessarily be helpful in distinguishing HFpEF from its mimics.[72] Conversely, many patients with HFpEF may also demonstrate no symptoms at rest, and their resting estimates of filling pressure may be normal or of borderline significance even after perturbation of their hemodynamic system.[10] This is particularly problematic in early-stage disease and in obesity-related phenotypes, where NP levels may also be suppressed and resting congestion may be very minimal.[54-55] Therefore, in cases of clinical conundrum, we would recommend more invasive hemodynamic testing, as opposed to non-invasive alternatives, to ensure that a diagnosis of HFpEF is not missed.

However, the biggest issue contributing to an underdiagnosis of the condition remains clinical inertia, which often amounts to missed opportunities in referrals.[2-4,6,50] HFpEF is often overlooked in the presence of mimicking non-cardiac comorbidities such as obesity, deconditioning, chronic lung disease, or anemia. In fact, these conditions frequently coexist with HFpEF and can even amplify the symptoms faced by patients, highlighting the need to address both HFpEF and comorbidities simultaneously.

Table 3. Treatment strategy for heart failure with preserved ejection fraction.

Treatment Domain	Therapy/ Intervention	Mechanism / Target	Clinical Benefit	Key Evidence
Comorbidity Management	Hypertension control	↓ afterload, ↓ vascular stiffness	↓ HF incidence, disease progression	SPRINT, HYVET
	Diabetes management	Metabolic modulation	Improves outcomes	SGLT2i preferred
	CKD management	Cardiorenal protection	↓ progression, improved outcomes	SGLT2i, finerenone
	CAD management	Anti-ischemic therapy	Symptom relief	No HFpEF-specific RCT
	AF management (rate/ rhythm control)	Improve filling & haemodynamics	↓ symptoms, potential ↓ hospitalization	CABANA, ATHENA (post-hoc)
Foundational GDMT	Loop diuretics	Volume control (decongestion)	Symptom relief, ↓ congestion	No mortality benefit; careful titration required
	SGLT2 inhibitors (empagliflozin, dapagliflozin)	Osmotic diuresis, improved energetics, anti-inflammatory, renal protection	↓ HF hospitalization, improved outcomes	EMPEROR-Preserved, DELIVER; cornerstone therapy
	MRA (spironolactone, finerenone)	Anti-fibrotic, anti-inflammatory, RAAS modulation	↓ HF hospitalization (selected patients)	TOPCAT, FINEARTS-HF
Phenotype-Specific Therapy	Cardiometabolic phenotype	SGLT2i, MRA, blood pressure control	Target inflammation, fibrosis	RAAS-driven phenotype
	Obesity phenotype (semaglutide, tirzepatide)	Weight loss, ↓ inflammation	↑ quality of life, ↑ exercise capacity	STEP-HFpEF, SUMMIT
Non-Pharmacological Therapy	Cardiorenal phenotype	SGLT2i ± MRA	Renal protection, ↓ congestion	Strong benefit across CKD spectrum
	AF phenotype	Rhythm control, anticoagulation	Improve symptoms, prevent stroke	Individualized approach

This table summarizes a practical, phenotype-oriented approach to HFpEF management, integrating comorbidity optimization, guideline-directed medical therapy, and phenotype-specific interventions. Heart failure (HF), chronic kidney disease (CKD), coronary artery disease (CAD), atrial fibrillation (AF), sodium-glucose cotransporter 2 (SGLT2), mineralocorticoid receptor antagonist (MRA), renin-angiotensin-aldosterone system (RAAS), angiotensin receptor neprilysin inhibitors (ARNI).

Treatment of Heart Failure with Preserved Ejection Fraction (Table 3)

Therapeutic Goals in HFpEF

Unfortunately, unlike HFrEF, there are no proven pharmacological therapies that have demonstrated a definitive reduction in cardiovascular mortality across clinical trials in the HFpEF population.[2-4,6,50] However, there has been a paradigm shift in the landscape of treatment surrounding HFpEF, moving from symptom management and comorbidities optimization, to now include pharmacotherapies with evidence in reducing HF-related events such as hospitalization, symptom improvement, functional capacity, and quality of life.

We encourage a structured approach in terms of management of HFpEF, which includes:

1. treatment of comorbidities and co-existing conditions,
2. guideline-directed medical therapy targeting shared neurohormonal and metabolic pathways, and
3. phenotype-based therapy tailored to dominant comorbid and pathophysiologic drivers.

1. Treatment of Comorbidities and Coexisting Conditions

Optimal management of comorbidities is fundamental in the management of HFpEF because they contribute to the underlying pathophysiology of the condition, as highlighted in an earlier section.[11-12,14,73] For example, evidence has shown that optimization in blood pressure

control improved cardiac remodeling and diastolic dysfunction, although the exact impact of treatment on LV remodeling largely depended on the extent of regression in hypertrophy, changes in LV loading conditions, the direct effect of the antihypertensive medication on the myocardium, and potentially alterations in coronary reserve.[73-75] There is also growing evidence in the use of therapeutic agents such as ARNI and Mineralocorticoid Receptor Antagonist (MRA) for the concomitant treatment of HFpEF and resistant hypertension, which would potentially help clinicians in prioritizing choice of anti-hypertensive therapies.[74-75] There has also been similar levels of benefit seen in HFpEF outcomes following optimal glycaemic control, management of ischemic heart disease, rhythm control strategies in AF, treatment of obesity and management of sleep apnoea in patients living with HFpEF.[14]

2. Fundamental Therapy Diuretics

Various therapeutic agents have now been shown to be beneficial in the management of HFpEF, which in fact have superseded previously developed treatments. Nevertheless, evidence for the use of diuretics, despite lacking randomized controlled trials, is unquestionable in the face of cardiac congestion, and diuretics remain the cornerstone of symptomatic management in HFpEF. Loop diuretics are recommended as first-line therapy for relief of both pulmonary and systemic congestion, with careful assessment and titration of the dose to avoid risk of renal dysfunction and electrolyte imbalances.[6,8-9,43] Interestingly, HFpEF patients may exhibit differential responses to diuresis, with predominant interstitial rather than intravascular fluid retention, necessitating individualized dosing strategies.[76] There is also emerging evidence surrounding the use of novel therapies, such as semaglutide, that led to lower use of decongestive therapies in the long term. These findings highlight the evolving role of decongestion beyond conventional diuretics, supporting a more integrated and phenotype-specific approach.[77]

SGLT2 Inhibitors

SGLT2 inhibitors are now considered fundamental and a foundational disease-modifying therapy for Heart Failure with mildly reduced Ejection Fraction (HFmrEF) and HFpEF, irrespective of T2DM status.[78-79] This was mainly based on consistent reductions in worsening HF events driven mainly by fewer HF hospitalizations in clinical trials such as EMPEROR-Preserved and DELIVER.[78-79] These studies led to guideline positioning in the 2022 AHA/ACC/HFSA guideline, where SGLT2 inhibitors received a Class IIa recommendation for both HFmrEF and HFpEF to reduce HF hospitalizations and cardiovascular events.[43] The 2023 Focused Update of the ESC HF Guidelines similarly recommends SGLT2 inhibitors for patients with HFmrEF/HFpEF to reduce HF hospitalization and cardiovascular death, with a higher Class Ia level of recommendation.[9]

Aldosterone Targeted Therapies

In the TOPCAT trial, spironolactone reduced HF hospitalizations following subgroup analysis, which differentiated patients from 'the Americas' from those randomized in Russia and Georgia.[80-81] However, it should be highlighted that the overall trial remains largely neutral in its primary outcomes. Nevertheless, the 2022 AHA/ACC/HFSA guidelines have provided a Class IIb recommendation for the use of steroidal MRAs in HFpEF, reflecting earlier mixed evidence and heterogeneity of benefit across HFpEF populations.[43] More recently, the FINEARTS-HF trial demonstrated evidence in the use of the non-steroidal MRA, finerenone, in significantly reducing composite endpoints of worsening HF events and cardiovascular death in patients with HFmrEF/HFpEF.[18,80-81] These results strengthen the biological and clinical rationale for aldosterone targeted therapies as potential disease-modifying therapy in HF, and have led to many more clinical trials being conducted in this space involving other agents such as vicadrostat and balcirenone in treating HF, agnostic to LVEF values.[80-81]

3. Phenotype-Based Treatment Cardio-Kidney-Metabolic (CKM) Syndrome and Obesity

The American Heart Association has since introduced a framework in the management of Cardio-Kidney-Metabolic (CKM) syndrome, owing to its exponential rise among communities globally.[82-83] It remains uncanny how treatment options available for the management of HFpEF greatly resemble those of diabetic and non-diabetic CKD, which emphasizes the large overlap in pathophysiological processes, centered around inflammation, fibrosis, hemodynamic and metabolic disturbances. As previously described, SGLT2 inhibitors and MRAs, specifically non-steroidal variants, have been shown to be beneficial in CKD, T2DM, and now HFpEF and should be prioritized when managing patients with such HFpEF phenotypes.

Obesity and adiposity, a progenitor in most cases of CKM syndrome, are equally important in HFpEF phenotypes. In the STEP-HFpEF trial, the use of semaglutide 2.4 mg weekly was shown to significantly improve symptoms and functional capacity in obese HFpEF patients.[83] There was improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) scores by 16.6 points in the intervention group, versus 8.7 points using placebo ($p<0.001$), with equally significant weight reduction (−13.3% versus −2.6% ($P<0.001$)) and 6-minute walk distance (21.5m versus 1.2m ($P<0.001$)). Another trial focused on T2DM patients, with HFpEF and obesity, confirmed similar benefits as well, and findings from both trials were further reinforced through a pooled analysis.[83] More recently, the SUMMIT trial demonstrated a significant reduction in composite endpoints of cardiovascular death and worsening HF (HR 0.62; 95% CI 0.41–0.95; P=0.026), alongside significantly improved KCCQ score (between-group difference 6.9 points; $P<0.001$) in HFpEF patients with obesity following the use of tirzepatide, a dual-incretin receptor agonist containing GLP1-RA and glucose-dependent insulinotropic polypeptide (GIP).[83]

These trials provide compelling evidence that obesity is a modifiable pathophysiologic driver rather than merely an associated condition. Alongside pharmacotherapeutics, patients living with HFpEF and obesity should also be considered for bariatric surgery, where limited data have shown improvements in symptoms, reverse LV remodeling, and lipidomic changes in HFpEF patients, albeit in a small cohort.[84] In addition, structured, supervised aerobic exercise training to improve functional capacity and quality of life should also be integrated into the holistic management of the disease.[85]

Coronary Artery Disease & Microvascular Dysfunction

Despite a plethora of evidence proving how prevalent both CAD and MVD are in patients living with HFpEF, there remains no strong evidence to support the routine use of coronary revascularization, anti-anginal, and microvascular-targeted therapies to confer benefit.[38-39,41-42] However, concomitant ischemia and chronic coronary syndrome can exist and should still be managed according to guidelines.[40]

Chronotropic Incompetence & Exercise Intolerance

Chronotropic incompetence is common in HFpEF and contributes to exercise intolerance.[26-27] Excessive heart rate reduction with BB or non-dihydropyridine calcium channel blockers may worsen exercise capacity in selected patients, and as alluded to in an earlier section, withdrawal of such therapies, specifically that of BB, has been shown to be beneficial in selected populations.[28] However, the role of rate-adaptive pacing in symptomatic HFpEF patients with chronotropic incompetence remains uncertain, following publication of opposing results from trials such as RAPID-HF and myPACE.[86] As such, we are unable to recommend routine pacemaker-based chronotropic therapy in HFpEF outside of established pacing indications.

Cardiac Rehabilitation (CR) is a clinically meaningful non-pharmacological intervention in HFpEF, addressing the core limitations of exercise intolerance and functional impairment.[87] Comprehensive CR programs, including structured exercise training, education, and lifestyle modification, have been shown to significantly improve exercise capacity, functional status, and health-related quality of life, while also providing effective symptom relief, particularly dyspnoea and fatigue. These benefits are highly relevant in HFpEF, where reduced physical capacity and poor quality of life are dominant clinical features. Supervised exercise-based CR further enhances adherence and outcomes, leading to greater improvements in peak oxygen uptake and daily functional performance.[87] Therefore, CR should be incorporated as an essential component of holistic HFpEF management, particularly in patients with exercise limitation and deconditioning.

Atrial Fibrillation

The CABANA trial demonstrated the effectiveness of catheter ablation in reducing all-cause mortality and improving quality of life compared with pharmacotherapy in patients with concomitant HF and AF.[88] However, insight from CABANA focusing on HFpEF revealed that patients with the condition experienced higher rates of recurrence post-procedure. This has been similarly demonstrated in other studies as well.[89-90] Rhythm control strategies should, thus, be individualized, and this further highlights the importance of adopting a holistic, multi-prong approach in the management of concomitant HFpEF and AF – tackling underlying comorbidities that can potentially drive both conditions while attempting to restore sinus rhythm.

HFpEF in Women

Recognition of the female-predominant HFpEF phenotype has important therapeutic implications, particularly surrounding neurohormonal

modulation. Among available therapies, ARNI appears especially relevant in this subgroup.[33-34] Although the PARAGON-HF trial did not meet its primary endpoint, prespecified subgroup analyses demonstrated a significant sex-specific benefit, with a substantial reduction in HF hospitalization among women, compared to men.[33-34] This differential response is biologically plausible as women, particularly post-menopausal, exhibit relative NP deficiency, heightened RAAS activation, and increased neprilysin activity related to adiposity, all of which can potentially be modulated by ARNI.[33-34] Therefore, ARNI may be preferentially considered in women with HFpEF, particularly those with cardiometabolic features such as obesity, hypertension, and elevated NP.

Implementation of HFpEF Diagnostic Pathways in Resource-Limited Settings

A common issue faced by many healthcare systems, particularly in low- and middle-income countries, includes poor accessibility to NP testing, diastolic stress echocardiography, and invasive hemodynamic assessment. It is therefore pivotal that our review article addresses potential diagnostic strategies for HFpEF that are adaptable, pragmatic, and grounded in clinical probability rather than dependence on advanced technologies. We highlight some common dilemmas and possible solutions, as follows.

Primary Care & Frontline Services Without Natriuretic Peptide Testing

In healthcare institutions where NP testing remains unavailable, clinical gestalt and probability assessment become paramount. Good history-taking remains important, especially in such circumstances, and primary care clinicians should recognize symptom patterns alongside features suggestive of high-risk clinical risk. Presence of older age, long-standing hypertension, obesity, T2DM, AF, and CKD in particular should alert clinicians regarding a high likelihood of HFpEF in the appropriate clinical context, especially when present together. This should also prompt an early referral for advance evaluation, even in the absence of biomarker confirmation.

In addition, basic clinical investigations remain valuable in this context to support clinical suspicion for the diagnosis. An abnormal electrocardiogram with features of LV hypertrophy, or a chest radiograph demonstrating pulmonary congestion or pleural effusion, supports a likely cardiac etiology and strengthens the case for referral, even without NP testing or an echocardiogram. Unremarkable baseline tests may lower suspicion but do not exclude HFpEF, particularly in patients with persistent or progressive symptoms. In such scenarios, this should still trigger a referral for specialist evaluation rather than prolonged observation in the ambulatory community setting.

Cardiology Evaluation Without Stress Echocardiography

Hesitance among cardiologists to perform stress echocardiography is often not due to a lack of equipment (stress echocardiography can be performed using a conventional exercise treadmill if a semi-supine bicycle is unavailable) but rather to a lack of awareness and expertise in performing and interpreting the test comprehensively. Furthermore, stress echocardiography using an exercise treadmill can be more cumbersome and time-consuming, requiring back-and-forth transfers between the bedside and the treadmill throughout the test. It is thus important to highlight that stress echocardiography for HFpEF diagnosis is not meant to be performed in all cases suspicious of HFpEF, but only in those with intermediate probability for the condition, and that probability-based diagnostic scores, as discussed above, are especially useful in this context. Patients with scores suggestive of a high probability of the disease may be diagnosed with HFpEF with reasonable confidence, without further testing.

However, in clinical settings where stress echocardiography is truly unavailable, cardiologists should maximize the diagnostic yield of the resting echocardiography performed and, when paired with diagnostic scoring tools, can reasonably follow patients with scores suggestive of intermediate risk for HFpEF closely in the ambulatory setting for changes in clinical context. It is also reasonable to consider pharmacotherapies that already have a clear indication in individual patients, especially in those with T2DM, CKD, or obesity, which may also be beneficial in patients who might have HFpEF. In settings where invasive hemodynamic testing is readily available, this is a reasonable alternative to aid the diagnosis of HFpEF in patients suspected of the condition.

Limited Access to Right Heart Catheterization

RHC with exercise remains the 'gold standard' for the diagnosis of HFpEF. However, the authors are cognizant that this service is largely unavailable

in many centers. As mentioned previously, non-invasive stress testing remains a reasonable alternative, and many do not pursue it mainly due to a lack of awareness and knowledge, which can largely be addressed through improved nationwide training. If RHC can be performed sans exercise, several methods to 'perturb the system' have been tested, including direct saline loading or passive leg raises, which can also be attempted. However, clinicians should be aware of the limited evidence supporting their use. It is also reasonable to consider a longitudinal diagnostic approach, with repeated clinical assessments, serial TTEs, evaluation of response to empiric therapy, such as cautious diuretic use, and monitoring of symptom trajectories, which can provide indirect confirmation over time, although this is often less than ideal. It should also be remembered that in certain clinical mimics, such as pulmonary hypertension or constrictive pericardial disease, invasive hemodynamic assessment can at times be crucial for confirmation of the diagnosis, and patients should be referred early to tertiary centers with capabilities to perform invasive hemodynamic testing, so as not to delay treatment.

Referral Networks and Stepwise Escalation

An effective strategy in resource-limited systems is the development of tiered referral networks, whereby primary and secondary care hospitals are encouraged to identify cases of suspected HFpEF early, and are also encouraged to refer complex or inconclusive cases to regional centers with the appropriate echocardiography or catheterization facilities and expertise. The path forward should include the development of a spoke-and-hub model, with clear referral criteria based on symptom burden, comorbidity profile, and resting echocardiographic findings, which could reduce referral delays and avoid redundant requests for investigations, thereby optimizing the use of limited resources.

Conclusion

HFpEF has evolved from a poorly defined clinical entity into one that is both heterogeneous and complex, driven by a diverse range of pathophysiological processes and associated with multimorbidity clusters. Although initial phenotyping exercises have been unnecessarily complicated, clinical phenotyping of HFpEF over the past decade has largely helped reshape the management paradigm of the condition by identifying key clinical manifestations of the disease. The existence of such phenotypes has also been largely supported by successful treatment options that have demonstrated consistent benefits in the HFpEF space.

As the evidence surrounding successful therapeutic agents expands, the importance of improving diagnostic accuracy to ensure patients are identified early and precisely so they can derive benefit from treatment grows. Accurate diagnosis requires a structured, probability-based approach that integrates clinical assessment, biomarker utilization, multimodality imaging, and hemodynamic assessment. Our review will hopefully provide guidance and a framework for managing HFpEF for clinicians in various clinical settings by bridging the gap between the pathophysiological complexity surrounding HFpEF and its effective clinical management.

List of Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
ARNI	Angiotensin Receptor Neprilysin Inhibitors
ATTR-CM	Transthyretin Cardiac Amyloidosis
BB	Beta-Blockers
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
CKM	Cardio-Kidney-Metabolic
ESC	European Society of Cardiology
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left Atrial Volume Index
LV	Left Ventricular
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
MAFLD	Metabolic-Associated Fatty Liver Disease
MRA	Mineralocorticoid Receptor Antagonist

MVD	Microvascular Dysfunction
NP	Natriuretic Peptides
PCWP	Pulmonary Capillary Wedge Pressure
RAAS	Renin-Angiotensin-Aldosterone System
RHC	Right Heart Catheterization
SGLT2	Sodium-Glucose Cotransporter 2
T2DM	Type 2 Diabetes Mellitus
TTE	Transthoracic Echocardiography
VO_2Max	Peak Oxygen Consumption

Ethical Clearance

No ethics approval was required in view of the nature of the article (i.e, review article). All tables and figures are the work of the main author and the co-authors and have not been previously published elsewhere or adapted from other materials previously or currently published.

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Case Reports

Cardiac Resynchronization Therapy (CRT) Optimization: A Way Out for Non-Responders - A Case Report

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Abstract

Background: Non-responders account for 30% of patients receiving Cardiac Resynchronization Therapy (CRT). Optimization of CRT using Electrocardiographic (ECG) and Transthoracic Echocardiographic (TTE) guidance has been proposed as a strategy to enhance therapeutic efficacy in this subset. This case report presents a young female patient with advanced heart failure secondary to ischemic cardiomyopathy, highlighting the role of ECG- and TTE-guided CRT optimization in improving clinical and hemodynamic outcomes.

Case Illustration: A 37-year-old female presented with advanced heart failure. Her medical history was notable for recurrent episodes of acute coronary syndrome, multiple Percutaneous Coronary Interventions (PCIs), and Cardiac Resynchronization Therapy with Pacemaker (CRT-P) implantation, despite adherence to Guideline-Directed Medical Therapy (GDMT).

On admission, the ECG demonstrated atrial sensing with consistent Biventricular (BV) pacing. Laboratory evaluation revealed an elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 5.462 pg/mL. TTE showed a severely reduced Left Ventricular Ejection Fraction (LVEF) of 20% and an absent A wave on mitral inflow Doppler, indicating impaired diastolic filling. Additionally, the Left Ventricular Outflow Tract (LVOT) Velocity Time Integral (VTI) was reduced to 7.4 cm, consistent with low forward stroke volume. Six months after the implantation, CRT optimization was performed using ECG and TTE guidance. Optimization resulted in a reduction of QRS duration to 129 ms, distinct separation of the mitral inflow E and A waves, an increase in LVOT VTI to 10.9 cm, and an improvement in functional capacity to New York Heart Association (NYHA) class III.

Conclusions: CRT optimization, guided by ECG or TTE, is critical in managing non-responders. In this case, it led to improved QRS duration, hemodynamics, and NYHA functional class. Routine reassessment should be considered in patients with persistent symptoms despite optimal GDMT to enhance clinical response.

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Keywords: Non-responder, CRT optimization, ECG guided CRT optimization, TTE guided CRT optimization.

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Introduction

Cardiac Resynchronization Therapy (CRT) is recommended for Heart Failure with reduced Ejection Fraction (HFrEF) with an expansive QRS complex because it improves myocardial function by resynchronizing myocardial contraction, resulting in reverse left ventricular remodeling.[1] However, almost one-third of patients are Non-Responders (NR), and only half of this group will survive four years after implantation.[2-3] NR is defined by one or more of the following criteria: worsening symptoms of heart failure after receiving CRT, no improvement in functional classification, and increased ventricular remodeling after 6 months of CRT placement, or worsening symptoms after previously responding.[4]

CRT optimization can be performed using several methods, such as Echocardiography (ECG)- or Transthoracic Echocardiographic (TTE)-guided approaches. TTE guidance can be achieved by assessing mitral inflow, Left Ventricular (LV) Outflow Tract (LVOT) Velocity Time Integral (VTI), which reflects the most significant stroke volume, tissue Doppler imaging (TDI), M-mode, or strain measurement. ECG guidance involves evaluating the QRS-based approach, 12-lead ECG, and Fusion-Optimized Intervals (FOI).[5]

This case presentation aims to describe CRT optimization guided by ECG and TTE in a patient with HFrEF secondary to ischemic cardiomyopathy.

Case Illustration

A 37-year-old female patient came to the emergency room with worsening symptoms of heart failure, such as shortness of breath, swelling in both legs, and a bloated stomach for one week before admission. She had a history of Acute Coronary Syndrome (ACS) in 2018 and 2020, underwent Percutaneous Coronary Intervention (PCI) with one Drug-Eluting Stent (DES) in the Left Anterior Descending (LAD) and Left Main-Left Circumflex (LM-LCx) in 2018 and 2021, respectively, and received a Cardiac Resynchronization Therapy Pacemaker (CRT-P) in April 2021. Her medications included Sacubitril/Valsartan 7 mg twice daily, Carvedilol 12.5 mg twice daily, Amiodarone 200 mg once daily, Furosemide 40 mg twice daily, Tolvaptan 7.5 mg twice daily, Atorvastatin 20 mg once daily, Spironolactone 25 mg once daily, Clopidogrel 75 mg once daily, and Aspirin 80 mg once daily.

Physical examination revealed increased jugular venous pressure, positive hepatojugular reflex, a pansystolic murmur 3/6 on the left lateral sternal border, rales in the lower third of the lungs, ascites, and pitting edema in both legs. ECG showed atrial sensing and Biventricular (BV) pacing (R wave in aVR and Rs in V1) with a QRS rate of 90 bpm and a QRS duration of 160 ms. Laboratory examination showed creatinine 1.23 mg/dl, Estimated Glomerular Filtration Rate (eGFR) 49, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) 5462 pg/ml. Chest X-ray revealed cardiomegaly with signs of congestion. Echocardiography showed a Left Ventricular Ejection Fraction (LVEF) of 20%, Tricuspid Annular Plane Systolic Excursion (TAPSE) of 1.6 cm, global hypokinesis, dilatation of all chambers, eccentric Left Ventricular Hypertrophy (LVH), moderate to severe Mitral Regurgitation (MR) due to the tethering of the Posterior Mitral Leaflet (PML), moderate Tricuspid Regurgitation

Table 1. CRT optimization with TTE guided.

	1	2	3	4	5	6	7	8	9
AV Delay (ms)	120/110	120/110	120/110	120/110	120/110	130/130 Syn AV on -30 ms	130/130 Syn AV on -20ms	130/130 Syn AV on - 10 ms	130/130 Syn AV on -10 ms
V-V synchrony (ms)	LV (D1/ mid2) to RV 0 ms (simultant)	LV (D1-mid2) to RV 30 ms	LV (D1-mid2) to RV 30 ms	LV (D1-mid2) to RV 60 ms	LV (D1-mid2) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV (D1-P4) to RV 30 ms
LVOT VTI (cm)	7.2	10.2	6.8	9.6	10.7	9.7	10.9	-	9.6
E/A	separated	separated	separated	separated	separated	separated	separated clearly, E/A 3.2	separated	separated
QRSd (ms)	321	153	167	129	129	129	129	128	151

AV: atrioventricular; CRT: Cardiac Resynchronization Therapy; D: Distal; LV: Left Ventricle; LVOT VTI: Left Ventricular Outflow Tract Velocity Time Integral; P: Proximal; QRSd: QRS duration; Syn: Synchrony; TTE: Transthoracic Echocardiography; VV: Ventriculo-Ventricular

(TR) with TVG of 26 mmHg, and mild Pulmonary Regurgitation (PR) with a Mean Pulmonary Arterial Pressure (mPAP) of 60 mmHg.

During hospitalization, the patient complained of fatigue, and her blood pressure dropped to 60/45 (50) mmHg, leading to adjustments in her antihypertensive medications. The first attempt at CRT-P optimization guided by TTE was planned six months after implantation. Multiple attempts at Atrioventricular (AV) delay, and Ventriculo-Ventricular (VV) synchrony settings using a programmer machine were performed simultaneously with the measurement of LVOT VTI and mitral inflow E/A using TTE, as well as the measurement of QRS duration using ECG. The optimal parameter for the CRT-P was a Syn AV offset of -20 ms and an LV pacing configuration from D1 to P4, with a 60 ms delay relative to right ventricular pacing. These AV delay and VV synchrony settings showed clearly separated E/A of 3.2, LVOT VTI of 10.9 cm, and QRS duration of 129 ms, as shown in Table 1 and Figure 1.

The patient's condition improved with a blood pressure of 90/56 (67) mmHg. One month after CRT optimization, she had stable hemodynamics and an improved New York Heart Association (NYHA) functional class, classified as III. ECG showed atrial sensing and BV pacing-fusion with a shorter QRS duration of 129 ms (Figure 2), and echocardiography revealed clearly separated E and A waves.

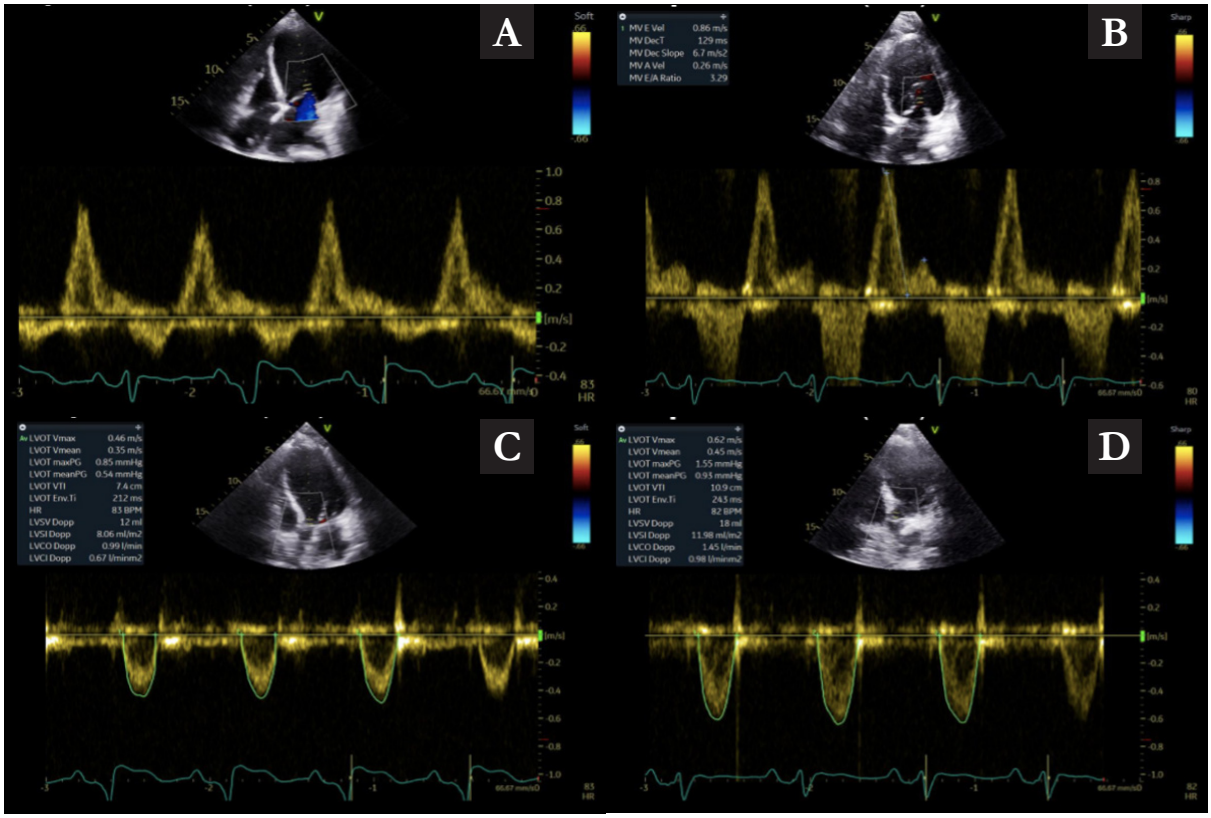

Figure 1. (A) E/A before CRT optimization; (B) E/A after CRT optimization; (C) LVOT VTI before CRT optimization; (D) LVOT VTI after CRT optimization.

Discussion

CRT is one of the most important treatments for drug-refractory heart failure. CRT aims to correct the three types of cardiac dyssynchronous activation through BV pacemaker stimulation, thereby improving LV hemodynamic and cardiac efficiency. CRT response is defined by three categories: clinical measurement assessment, LV reverse remodeling assessment, and outcome measure assessment. It has been suggested that response rates are higher when clinical measures are used rather than LV remodeling or outcome measures. Additionally, several factors have been associated with a greater benefit from CRT, including female sex, QRS width >150 ms, Left Bundle Branch Block (LBBB) morphology, and non-ischemic etiology.[4,6]

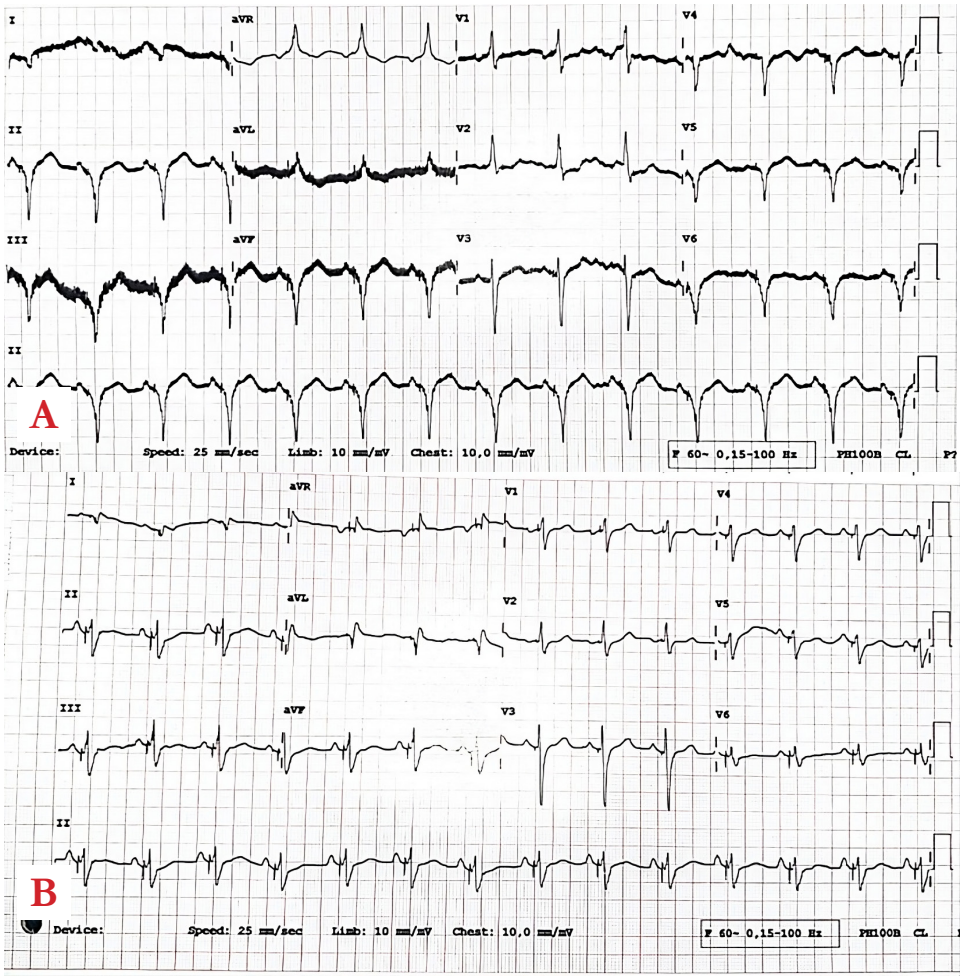

Figure 2. ECG before (A) and after CRT optimization showing BV pacing – fusion with shorter QRS duration (B).

This case highlights the uncommon presentation of ischemic cardiomyopathy in a young female patient. While younger age is generally associated with better outcomes in CRT, factors such as myocardial fibrosis, left ventricular lead positioning, and the underlying etiology of cardiomyopathy can significantly influence the response to therapy.[7] The patient was considered a non-responder due to worsening symptoms even after CRT placement, with NYHA class IV criteria. Additionally, LV reverse remodeling assessment in the acute setting showed an LVOT VTI of 7.4 cm, resulting in low cardiac output. Outcome measurement indicated hospitalization due to acute heart failure. Therefore, optimization of CRT was needed to address these issues. The ischemic cardiomyopathy etiology of the heart failure in this patient resulted in less benefit from CRT.

In ischemic cardiomyopathy, non-response to CRT is commonly attributed to two key factors, namely high myocardial scar burden and limited mechanical recruitment. Extensive or transmural scar tissue limits both electrical capture and mechanical contraction, reducing CRT efficacy. Furthermore, despite successful restoration of electrical synchrony, regions of non-viable myocardium exhibit diminished contractile reserve, thereby attenuating the hemodynamic efficacy of CRT.[8] Therefore, in CRT candidates with ischemic cardiomyopathy, pre-implant viability imaging and scar assessment using Cardiac Magnetic Resonance (CMR), nuclear imaging, or Computed Tomography (CT) are essential for predicting response and guiding lead placement.[9]

Several factors beyond pre-implant patient selection may affect CRT response, including peri-implant lead positioning and lead choice, as well as post-implant factors related to the device and heart failure therapy. Among the many factors contributing to suboptimal CRT response, suboptimal AV timing is the most prevalent. Suboptimal AV timing can be managed through AV and VV optimization using

TTE, ECG, or device-based methods.[10]

Simplified Doppler screening for AV optimization can be performed using pulsed Doppler mitral inflow. AV optimization is recommended if any of the following are observed: the A wave is not identified, the E and A waves are merged, or the A wave is truncated by mitral closure.[11] As shown in this patient's TTE, the A wave was not identified on pulsed Doppler mitral inflow; therefore, AV optimization was required. AV optimization can also be achieved by optimizing LV systolic performance through evaluation of the aortic pulsed-wave Doppler VTI, which correlates with LV stroke volume. Aortic VTI is measured across a range of AV delays, and the delay that yields the most significant increase in VTI is selected as the optimal AV delay.[11-12] The AV delay that was set at -20 ms was considered the setting that led to the greatest LVOT VTI of 10.9 cm compared to the baseline of 7.4 cm.

VV optimization can also be performed using the aortic VTI method, as in AV delay optimization. In this method, aortic VTI is measured at varying intervals of RV and LV preexcitation, with the interval that yields the greatest VTI selected as the optimal VV delay.[12]

ECG provides an additional method to optimize CRT by adjusting both AV and VV delays. ECG parameters used to measure ventricular dyssynchrony include QRS duration and the presence of LBBB. ECG methods for optimizing CRT include the twelve-lead ECG and FOI. The twelve-lead ECG is used to evaluate the morphology rather than the QRS duration of the BV-paced complex. A stepwise increase in AV delay during BV-pacing begins with a short AV delay to identify the onset at which QRS morphology changes. Meanwhile, VV interval programming should be used to create a QRS complex with adequate contribution from LV pacing to maintain a dominant R (R, Rs, or RS pattern) in leads V1-V2.

The FOI method involves finding the fusion band. During atrial sensing, the AV interval is progressively shortened with LV pacing only, starting with the most extended AV interval that allows capture, then decreasing of 20 ms until the AV interval produces only LV capture. The AV interval that provides the narrowest QRS is considered the fusion-optimized AV interval. This is followed by adjusting the VV interval during atrial sensing and comparing QRS duration across configurations. The VV value that obtains the narrowest QRS is considered the fusion-optimized VV interval.5 In this patient, a CRT-P setting of Syn AV on -20 ms and LV (D1-P4) to RV 60 ms led to the shortest QRS duration of 129 ms.

Fusion with intrinsic rhythm during pacing will exhibit three activation fronts compared to the usual pure BV pacing. This fusion pacing is superior to any optimized BV configuration, resulting in improved LV and RV performance.[5] The patient's ECG after CRT optimization showed BV-fusion pacing with a shorter QRS duration of 129 ms than before CRT optimization. The importance of shortening QRS duration can predict a favorable prognosis in patients with LBBB, which is associated with more than two times lower mortality rates. It also serves as a biomarker for the reduction or elimination of asynchronous contraction caused by LBBB. It is a strong predictor of reverse LV electrical remodeling, indicating that the initial goal of CRT implantation has been achieved.[13]

Routine follow-up evaluations should be conducted at 3 months post-implantation and every 6 months thereafter. However, if a persistently widened QRS complex is observed during pacing, incidental optimization of device settings should be considered.[14] Studies have demonstrated that CRT significantly prolongs the time to recurrent hospitalization due to heart failure or all-cause mortality, irrespective of the underlying etiology of cardiomyopathy.[15] In patients with persistent non-response to CRT, several advanced interventions may be considered. Multipoint Pacing (MPP) enhances resynchronization by delivering stimuli from multiple sites within the left ventricular myocardium.[16] Conduction System Pacing (CSP), including His bundle and left bundle branch area pacing, offers a more physiologic alternative to traditional BV pacing.[17] Left ventricular lead repositioning, guided by imaging, can also improve response by targeting viable myocardium and areas of latest activation.[18] In addition, ongoing titration and optimization of Guideline-Directed Medical Therapy (GDMT) remain essential to enhance clinical outcomes.[19]

The integration of ECG and TTE techniques for CRT optimization proves highly valuable, especially in settings with limited resources where access to advanced imaging is restricted. This combined method provides a practical and efficient means to improve CRT efficacy and clinical outcomes under such constraints.

Conclusion

CRT optimization, whether guided by ECG or TTE, is required for managing non-responders. In this case, it resulted in clinical and hemodynamic improvements, including a reduction in QRS duration, enhancement of LVOT VTI, and an improvement in functional status. It is essential to screen for the need for CRT optimization, particularly in patients with refractory heart failure despite optimal GDMT, to enhance clinical response.

List of Abbreviations

ACS	Acute Coronary Syndrome
AV	Atrioventricular
BV	Biventricular
CMR	Cardiac Magnetic Resonance
CRT	Cardiac Resynchronization Therapy
CRT-P	Cardiac Resynchronization Therapy with Pacemaker
CSP	Conduction System Pacing
CT	Computed Tomography
DES	Drug-Eluting Stent
ECG	Electrocardiography
eGFR	Estimated Glomerular Filtration Rate
FOI	Fusion-Optimized Intervals
GDMT	Guideline-Directed Medical Therapy
HFrEF	Heart Failure Reduced Ejection Fraction
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LCx	Left Circumflex
LM	Left Main
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MPAP	Mean Pulmonary Arterial Pressure
MPP	Multipoint Pacing
MR	Mitral Regurgitation
NYHA	New York Heart Association
NT-proBNP	N-terminal pro–B-type natriuretic peptide
PCI	Percutaneous Coronary Intervention
PML	Posterior Mitral Leaflet
TAPSE	Tricuspid Annular Plane Systolic Excursion
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TVG	Tricuspid Valve Gradient
VTI	Velocity Time Integral
V-V	Ventriculo-Ventricular

Ethical Clearance

Informed consent has been obtained from the patient to publish this case report.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

NED performed the literature search and drafted the original manuscript. DYH supervised the project, and critically revised the manuscript for important intellectual content. Both authors have read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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Case Reports

Acute Bilateral Limb Ischemia in Peripartum Cardiomyopathy: An Often Overlooked Complication

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Abstract

Background: Peripartum Cardiomyopathy (PPCM) is a specific subset of systolic heart failure with potentially devastating complications. Thromboembolism, of complication, requires careful evaluation to assess risk and guide management. This case report of acute limb ischemia complicating peripartum cardiomyopathy is an example of how to deal with thromboembolism in PPCM.

Case Illustration: A 42-year-old woman presented with clinically decompensated heart failure, which started three weeks after her second childbirth and had been worsening over the last four months. At presentation, pulmonary and extremity congestion was evident. Echocardiography revealed a dilated heart and reduced LVEF of 23%. She was diagnosed with PPCM and treated accordingly. On the first night in the ward, she felt sudden pain and paresthesia in her right foot. The distal pulses were weakly palpable, and there was hypoesthesia of the toes. Duplex ultrasound found fresh thrombi in the bilateral popliteal arteries. Diagnosis of acute limb ischemia was confirmed, warranting the use of anticoagulants aside from her existing heart failure medications. Symptoms continued to improve until discharge.

Conclusions: A case of a 42-year-old woman diagnosed with PPCM suffering from an acute thromboembolic episode was reported. Risk assessment is essential for predicting the risk of future thromboembolism and implementing preventive measures. Different anticoagulants are indicated for different PPCM patient profiles, and careful consideration of their safety profiles in this population is needed.

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Keywords: PPCM, thromboembolism, risk assessment, anticoagulant.

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Introduction

Peripartum Cardiomyopathy (PPCM) is a specific form of systolic heart failure with potentially life-threatening complications, one of which is thromboembolism. Peripartum women are in a hypercoagulable state, predisposing them to stasis of blood, which ultimately leads to thromboembolic events that may present in various forms, from acute arterial thrombosis to cardioembolic stroke. In a cohort of the global PPCM registry by the European Society of Cardiology (ESC) EURObservational Research Programme, thromboembolism occurred in 6.8% of women, whereas the US IPAC Cohort reported a 6.6% of thromboembolism. At our center, there were 37 cases of PPCM from 2017-2022; 3 of them had manifestations of thromboembolism in various forms.

Case Illustration

A 42-year-old woman came to our Emergency Room with the chief complaint of breathlessness that worsened over the last week. She had difficulty sleeping at night due to positional dyspnea, nausea, and decreased tolerance of activity. Both of her legs were markedly swollen, although she had no complaints of foot ache or paresthesia at that time.

Her Heart Rate (HR) at admission was 112 bpm, blood pressures were 147/96 mmHg, respiratory rate was 26 x/minute, and peripheral oxygen saturation was 96% on room air. On physical examination, there was elevated jugular venous pressure, rales on lung auscultation, and slight hepatomegaly. Pitting edema was also found on both legs.

Her Electrocardiogram (ECG) at presentation revealed sinus tachycardia (HR 121 bpm), Left

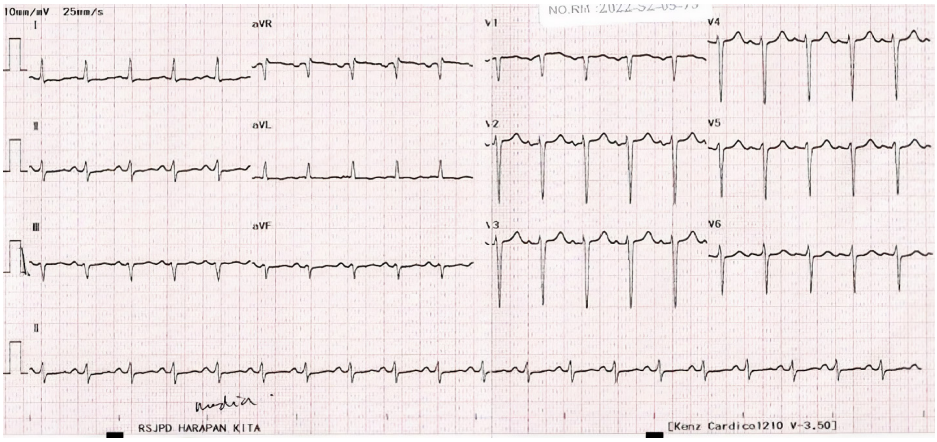

Figure 1. ECG at presentation showed sinus tachycardia and LVH with poor R wave progression.

Ventricular Hypertrophy (LVH), and poor R-wave progression. Bedside echocardiography revealed a dilated heart with Left Ventricular End-Diastolic Diameter (LVEDD) of 56 mm and markedly reduced ejection fraction (LVEF) of 29%. Right Ventricular (RV) function was normal with a Tricuspid Annular Plane Systolic Excursion (TAPSE) of 17 mm. No intracardiac thrombus was seen on bedside echocardiography examination. Routine laboratory results were within normal limits; however, NT-ProBNP was elevated at 3033.

On further history-taking, these symptoms started three weeks after delivering her second child, which was four months before. The pregnancy and delivery itself were uncomplicated. She was already on heart failure medications (bisoprolol 1.25 mg, spironolactone 25 mg, ramipril 5 mg, and furosemide 40 mg), although not routinely, because she was not keen on the diuretic effect. She also received a monthly injection of birth control therapy. Recently, she was hospitalized due to the worsening of her complaints and was discharged with some improvement of symptoms.

Initial diagnosis at admission was Acute Decompensated Heart Failure (ADHF) due to PPCM with moderate severity, and she was admitted to the general ward. IV furosemide was given at the rate of 5mg/hour, and she resumed her previous medications with the addition of warfarin 2 mg and prescription of bromocriptine 2.5 mg bid.

The next day, she underwent comprehensive echocardiography, which revealed a markedly dilated heart with an LVEDD of 62.9mm, a Left Ventricular End-Systolic Diameter (LVESD) of 56.2mm, and a Left Ventricular Ejection Fraction (LVEF) of 23%. RV function was normal, and still no intracardiac thrombus nor Spontaneous Echo Contrast (SEC) was found.

On her first night in the ward, she experienced sudden pain in her right foot with a Visual Analog

Scale (VAS) score of 8/10, accompanied by paresthesia and hypoesthesia of the medial toes. She had cold sweat, and the distal pulsation was weak. However, motoric function was normal, and neurologic examination confirmed hypoesthesia on the affected foot. Laboratory examination revealed a hypercoagulable state with D-dimer level at 4090, fibrinogen of 419, INR of 1.11, and A1C of 6.8. Liver functions were within normal limits. Doppler ultrasound showed fresh thrombi on both her popliteal arteries (left and right) with still some flow to the distal legs, and a diagnosis of acute bilateral limb ischemia was confirmed.

She was then transferred to the intermediate ward for observation and started on heparinization with Low Molecular Weight Heparin (LMWH) (enoxaparin at 0.6mg subcutaneous bid injection). Paracetamol as a pain reliever was administered, along with medications with anti-inflammatory and antioxidant properties (pentoxifylline 1200 mg, allopurinol 300 mg tid, bicarbonate 500 mg tid, and vitamin E 400 mg bid). She showed improvement of symptoms over the first day of diagnosis. She was immediately consulted for surgery for surgical revascularization. On further assessment by the surgeon, she did not need surgery and was advised to continue heparinization.

She continued to show improvements of both ischemic leg symptoms and heart failure symptoms. Her leg examination on the seventh day revealed improvement of flow in lower leg arteries, warm legs, and no neurological deficits on both legs. There were no more rales in both lungs, pitting edema of the legs had resolved, and the liver had returned to standard size. She achieved a 300 m distance on a 6-minute walk test, confirming complete decongestion. She was discharged on the seventh day on the following medications: furosemide 40 mg, bisoprolol 5 mg, candesartan 16 mg, spironolactone 50 mg, aspirin 80 mg, atorvastatin 80 mg, warfarin 2 mg, and metformin 500 mg.

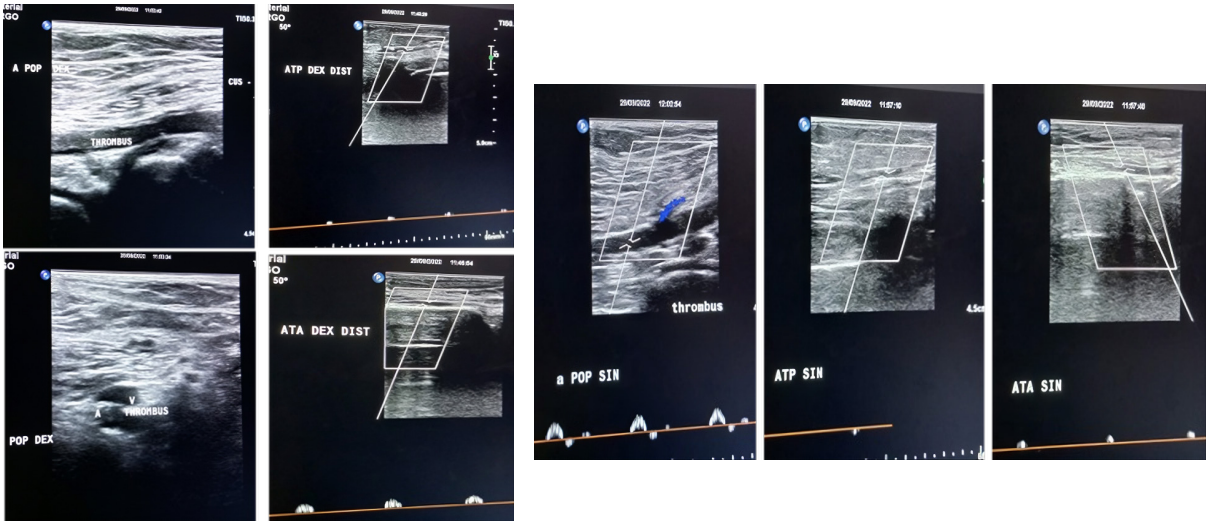

Figure 2. Duplex ultrasound of the lower limb showed fresh thrombus in the bilateral popliteal arteries. The flow is diminished in the distal artery in both legs.

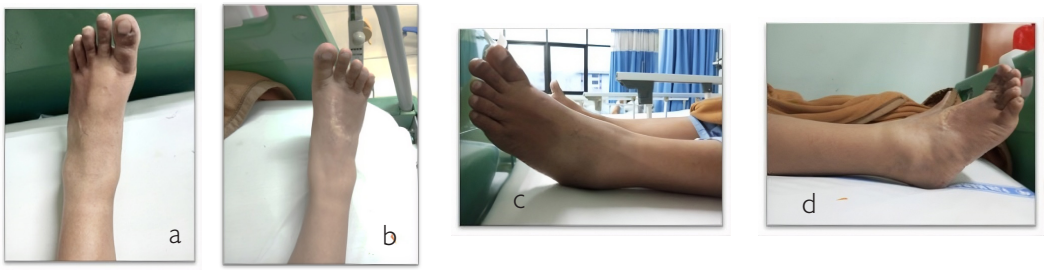

Figure 3. Clinical pictures of the patient's foot. (b) and (d) right foot, the affected side, appeared paler than the left foot (a) and (c).

Discussion

Our patient was initially diagnosed with PPCM. During the course of her disease, she suffered from an acute thromboembolism event manifesting as acute limb ischemia. Various factors are at play in the pathophysiology of thromboembolism in this patient, such as the peripartum period, acute heart failure due to PPCM, and the use of hormonal contraception.

Pathophysiology of Thrombosis in PPCM

PPCM is a specific subset of left heart failure occurring in women in their late pregnancy to the peripartum period. Currently, there is no comprehensive registry of PPCM in Indonesia. However, an observational study by Prameswari et al in 2016 revealed that 26% out of 305 women with pregnancy and cardiovascular complications were diagnosed with PPCM in Bandung, Indonesia.[1] At our center alone, there were 37 cases of PPCM during 2017-2021.

Our patient presented with an acute heart failure presentation, respiratory insufficiency, elevated NT-ProBNP, and LVEF at 23%, all of which pointed to her symptoms being categorized as "moderate" according to the 2019 ESC Position Statement on PPCM by Bauersach J et al.[3] This position statement also recommended that the mainstay treatment of PPCM was promoted under the tag "BOARD" therapy, consisting of bromocriptine, oral heart failure drugs, anticoagulants, vasorelaxants, and diuretics.

On the first night in the hospital, she experienced sudden pain and paresthesia in her right foot. Duplex ultrasound revealed fresh thrombosis in her right and left popliteal arteries, despite an asymptomatic left leg. She was diagnosed with acute limb ischemia and was promptly started on LMWH enoxaparin 0,6 mg subcutaneously. Bromocriptine was not given yet at this point and was withheld.

Thromboembolism is one of the most debilitating complications of PPCM. Women in general were at higher risk of thromboembolism compared to men, due to the pro-thrombotic nature of the hormone estrogen. This risk increases tenfold during pregnancy and up to twenty-fivefold in the postpartum period. Various mechanisms have been proposed to explain this predisposition, all of which contribute to Virchow's Triad of Pregnancy. Although traditionally used in the context of Venous Thromboembolism (VTE), this concept can be applied to arterial thromboembolism in the PPCM population, as the risk of both is similar in this population.[4]

The three elements of Virchow's Triad are all present during pregnancy and the postpartum period. Blood stasis, which begins in the first trimester and reaches its peak on the 36th week, is caused by progesterone-induced vasodilation and compression of blood vessels by the gravid uterus. Vascular damage is caused by delivery, both vaginal and assisted C-section. A hypercoagulable state during pregnancy is progressively activated to prepare for the challenge of delivery. Procoagulant activity is increased by heightening concentrations of fibrinogen and factors V, VIII, IX, and X, enhancing production of thrombin. Thrombus dissolution is reduced by decreasing the activity of tissue plasminogen activator (tPA) and increasing the activation of its inhibitors, types 1 and 2. All these resulted in increased risk of thromboembolism in pregnant and postpartum women.

A change in coagulable status of postpartum women increases the risk of thromboembolism. This hypercoagulable state was caused by changes of various thrombotic factor parameters, which take different times to return to baseline levels after delivery. Some parameters, such as factor VIII and von Willebrand factor, return to baseline within 72 hours postpartum, whereas others, such as the reduction in protein S, take several weeks to recover. In general, it is assumed that the hypercoagulability state is resolved after 6 weeks postpartum.[13] However, the risk of thrombosis may persist beyond 6 weeks. A study by Kamel H et al. in 2014 found that thromboembolic risk is highest during the first 6 weeks, remains significantly elevated through 15 weeks, and then declines. This is consistent with findings of laboratory markers, most of which return to baseline by the sixth week, whereas some remain abnormal through at least 12-15 weeks postpartum.

Our patient presented at four months postpartum (16 weeks), yet she suffered from an acute thromboembolic event. As her coagulable state is likely to return to baseline by this time, other factors may contribute to the development of arterial thrombosis.

Echocardiography of our patient revealed a low LVEF of 23% and a dilated heart, predisposing her to a condition of arterial stasis and increased risk of thromboembolism, as stated by Agarwal et al in 2019. In PPCM, there is also endothelial injury and immobilization due to heart failure symptoms. All these contribute to a condition of increased thromboembolism risk.

Risk Assessment of Thromboembolism in PPCM

The well-known Wells Score, widely used to assess thromboembolic risk, cannot be applied in the pregnant population.[5] To address these risks, the Royal College of Obstetricians and Gynecologists (RCOG) issued a guideline in 2015 stating that all women should undergo a documented assessment of risk factors for thromboembolism in early pregnancy or pre-pregnancy.[6] The guideline included a risk-scoring system to guide risk assessment and management in this vulnerable population, as depicted in Table 1.

Our patient admittedly did not undergo such a risk assessment in her previous pregnancy. Although she stated that the pregnancy and delivery itself were uneventful and uncomplicated, she should still be assessed accordingly. When this RCOG risk-scoring system was applied to our patient, she scored 5, indicating a "high risk". Admittedly, this is because she had a medical comorbidity of heart failure, which alone contributed 3 points to her score. But excluding the comorbidity, she still scored two due to her age (>35) and obesity, with a Body Mass Index (BMI) of 29.1. This rendered her at "intermediate risk," which, according to the guideline, should be managed with prophylaxis LMWH during pregnancy and the peripartum period for at least 10 days postpartum. The recommended dosing of LMWH is depicted in Table 2.

Table 1. Risk Scoring of Thromboembolism in pregnant and peripartum women by RCOG, 2018.

Pre-existing risk factors	Tick	Score
Previous VTE (except a single event related to major surgery)	☐	4
Previous VTE provoked by major surgery	☐	3
Known high-risk thrombophilia	☐	3
Medical comorbidities (e.g., cancer, heart failure, active SLE, inflammatory polyarthropathy or inflammatory bowel disease, current IV drug user)	☐	3
Family history of unprovoked or estrogen-related VTE in a first-degree relative	☐	1
Known low-risk thrombophilia (no VTE)	☐	1
Age >35 years	☐	1
Obesity	☐	1 or 2
Parity >= 3	☐	1
Smoker	☐	1
Gross varicose veins	☐	1
Obstetric risk factors		
Pre-eclampsia in the current pregnancy	☐	1
ART/IVF (antenatal only)	☐	1
Multiple pregnancy	☐	1
Caesarean section in labour	☐	2
Elective caesarean section	☐	1
Mid-cavity or rotational operative delivery	☐	1
Prolonged labour (>24 hours)	☐	1
PPH (>1 litre or transfusion)	☐	1
Preterm birth <37 weeks in current pregnancy	☐	1
Stillbirth in the current pregnancy	☐	1
Transient risk factors		
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g., appendectomy	☐	3
Hyperemesis	☐	3
OHSS (first trimester only)	☐	4
Current systemic infection	☐	1
Immobility, dehydration	☐	1

VTE: Venous Thromboembolism ; SLE: Systemic Lupus Erythematosus; ART/IVF: Assisted Reproduction Therapy/In Vitro Fertilization; PPH: Post-Partum Haemorrhage; OHSS: Ovarian Hyperstimulation Syndrome

Table 2. LMWH doses by RCOG Guideline.

Weight	Enoxaparin Doses
<50 kg	20 mg daily
50-90 kg	40 mg daily
91-130 kg	60 mg daily (may be divided into two doses)
131-170 kg	80 mg daily (may be divided into two doses)
>170 kg	0.6 mg/kg/day (may be divided into two doses)
High prophylactic dose for women 50-90 kg	40 mg 12-hourly

LMWH is the agent of choice for thrombosis prophylaxis in the pregnant and postpartum population. A 2011 study by Lindqvist et al. found a 88% relative risk reduction of 88% in obstetric patients with prior VTE who were given LMWH.[7] It does not cross the placenta (except fondaparinux, which crosses the placental barrier in small amounts) and is mainly eliminated by renal clearance. Doses should be adjusted in patients with renal failure; alternatively, unfractionated heparin (UFH) can be considered. Vitamin K Antagonist (VKA) is not safe for pregnant women because of fetal toxicity. Women on long-term VKA should be counseled to stop the drug before the 6th week of gestation to eliminate the risk of warfarin embryopathy.[8]

The Role of Bromocriptine in PPCM

Bromocriptine, a dopamine antagonist, has been widely studied as a new disease-specific therapy for PPCM. It works by inhibiting prolactin release, which is believed to have an essential role in PPCM pathophysiology. Under conditions of elevated reactive oxygen species (ROS) in late pregnancy and the peripartum period, the peptidase Cathepsin D is released, cleaving the hormone prolactin into its of kDa antiangiogenic fragment.[9] A study by Hilfiker-Kleiner et al. in 2017 reported a higher rate of LVEF recovery at 6 months in patients treated with bromocriptine than in those who were not.[10-11] However, this drug is pro-thrombotic in nature and has been reported to be linked to cerebrovascular ischemia and acute myocardial infarction in previous case reports.[12-13] Therefore, bromocriptine use in PPCM should always be accompanied by anticoagulation, at least at a prophylactic dose.

Our patient was prescribed bromocriptine 2,5 mg bid, planned to be given for two weeks, along with warfarin 2 mg as a prophylactic anticoagulant. However, before the administration of its first dose, the patient experienced an acute thromboembolic event in both her legs. Needless to say, bromocriptine was promptly stopped, and LMWH was administered.

Acute Limb Ischemia in PPCM

Thromboembolism in PPCM may present in multiple forms, the most common being thrombi in the left and right cardiac chambers. A study in Senegal reported that up to 30% of PPCM cases had LV thrombi.[15] There were also reported cases of multiple intra-abdominal thromboemboli[16], pulmonary embolism[17-18], cardioembolic stroke[19], and lower extremity arterial thromboembolism, which, in a case report by Carlson KM et al, was a presenting complaint of PPCM instead of heart failure.[20] At our center, there were three cases of thromboembolism complicating PPCM over the past 5 years. The presentations were acute cerebral ischemia caused by suspected cardiac emboli, acute limb ischemia, and acute pulmonary embolism.

The pathophysiology of lower-limb thromboembolism in PPCM, as highlighted by Isezuo et al., is linked to the hypercoagulable state of the peripartum period, ventricular dilatation, and hypokinesis observed in this subset of patients. Intracardiac thrombosis due to low ventricular ejection fraction was often thought to be the culprit, as reported in a case report.[21]

Our patient had an episode of acute thrombosis in the legs, manifesting as sudden foot pain and paresthesia. Duplex ultrasound of the legs revealed fresh thrombi in the bilateral popliteal arteries. She was diagnosed with acute limb ischemia stage I based on Rutherford classification, promptly given LMWH, and referred for surgery for urgent surgical revascularization. According to the 2017 ESC Guideline of Peripheral Arterial Disease, revascularization with endovascular therapy is preferred to surgical thrombectomy/bypass, owing to reduced morbidity and mortality. However, there are many considerations before deciding which method works best for each case, some of

them being the presence of a neurological deficit, ischaemia duration, its localization, comorbidities, type of conduit (artery or graft), and therapy-related risks and outcomes.[22]

Management of Acute Limb Ischemia

TASC-II Consensus on Management of Peripheral Arterial Disease recommends endovascular treatment for infrainguinal lesions.[23] However, Percutaneous Transluminal Angioplasty (PTA) was not readily available in our center, so surgery was the method of choice. The patient demonstrated clinical improvement on the surgical team assessment, and the surgery was ultimately deferred.

Her symptoms improved rapidly after analgesics and heparinization. Pulsation was palpated more strongly on the right foot, paresthesia and hypoesthesia were gone, and the VAS Score went down to 2/10. Surgery was withheld, and she continued to receive LMWH for 5 days, during which heart failure medications were optimized.

Choosing LMWH as an anticoagulant in this patient is based on multiple considerations. Zhu et al. proposed different anticoagulant regimens for different cardiomyopathy profiles of.[24] In the PPCM population, LVEF below 45% warrants administration of VKA, provided that the patient is in the late trimester of pregnancy or after delivery. Patients with other comorbidities such as atrial fibrillation, previous thromboembolism, or cardiac emboli were recommended to be given LMWH, as was the case with our patient. Novel Oral Anticoagulants (NOAC) such as rivaroxaban, apixaban, or dabigatran are generally avoided during pregnancy and the lactation period due to a lack of available safety data.

On the seventh day of admission, she had completed decongestion, as evidenced by a six-minute walk test distance >300 m. Pain in the leg had also resolved, and duplex evaluation demonstrated

Table 3. Anticoagulation of choice for patients with cardiomyopathy. From Zhu et al, 2021.

	Concomitant AF	Enlarged LAD	Previous TE/ evident intracavitary thrombus	Ventricular dilatation/ dysfunction, LVAA	Using bromocriptine
HCM	OAC recommended	OAC considered in obstructive HCM with LAD >=48 mm	-	OAC suggested in HCM with LVAA	-
DCM	OAC recommended as CHA2DS2-VASc score >=1	-	Anticoagulant therapy suggested	-	-
RCM	OAC suggested	-	OAC suggested	-	-
CM	VKA or direct thrombin inhibitors are recommended	-	VKA or direct thrombin inhibitors are recommended	-	-
HES	-	-	VKA recommended	-	-
ARVC	OAC considered	-	OAC recommended	-	-
LVNC	VKA preferred	-	VKA preferred	VKA preferred as LVEF <40%	-
TTS	-	-	Heparin (IV/SC)/ VKA/NOACs recommended	Heparin/VKA/NOACs considered if LVEF <= 30%, or large LVD involving apex	-
PPCM	LMWH recommended, VKA might be considered during lactation or during the 2nd/3rd trimester	-	LMWH recommended, VKA might be considered during lactation or during the 2nd/3rd trimester	LMWH suggested if LVEF <45%, VKA might be considered during lactation or during 2nd/3rd trimester	Heparin recommended

AF: Atrial Fibrillation; LAD: Left Atrial Diameter; TE: Thromboembolism; LVAA: Left Ventricular Apical Aneurysm; HCM: Hypertrophic Cardiomyopathy OAC: Oral Anticoagulation/Oral Anticoagulant; DCM: Dilated Cardiomyopathy; CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age ≥75 (2 points), Diabetes mellitus, Stroke/TIA/systemic embolism (2 points), Vascular disease, Age 65–74, Sex category; RCM: Restrictive Cardiomyopathy; CM: Cardiomyopathy; VKA: Vitamin K Antagonist; HES: Hypereosinophilic Syndrome; ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy; LVNC: Left Ventricular Noncompaction; LVEF: Left Ventricular Ejection Fraction; TTS: Takotsubo Syndrome; IV: Intravenous; SC: Subcutaneous; NOACs: Non–Vitamin K Oral Anticoagulants; LVD: Left Ventricular Dysfunction; PPCM: Peripartum Cardiomyopathy; LMWH: Low-Molecular-Weight Heparin.

improved flow in the distal leg arteries. She was discharged on optimal heart failure medications, atorvastatin, warfarin as an anticoagulant, and aspirin as an antiplatelet.

Contraceptive Measures in PPCM and Risk of Thromboembolism

On discharge, she was counseled on prognosis and subsequent pregnancy. Previously, she had been on a monthly injection of birth control, containing a combination of estrogen and progestin. The hormone estrogen is strongly associated with prothrombotic effects, affecting various factors in the coagulation and fibrinolysis cascade.[25]

A review by Abou-Ismail et al in 2020 found that women on combined oral contraception had an increased absolute risk of venous and arterial thromboembolism. There is currently little evidence evaluating the risk of thromboembolism in women using combined injectable contraceptives, like our patient. However, since any form of estrogen is contraindicated in patients with cardiac disease, it is reasonable to advise patients on other methods of birth control. A survey by Rosman L, et al revealed the three most common contraceptives used by women with PPCM are tubal ligation, condoms, and Intrauterine Device (IUD).[26] These long-acting reversible contraceptives are the most effective, and since they have little risk of thromboembolism, they should be the first choice for women with PPCM. Our patient was advised and agreed to the placement of an IUD device as her future contraceptive.

Conclusion

A case of acute limb ischemia complicating peripartum cardiomyopathy has been presented. There is an increased risk of thromboembolism in the PPCM population, which may manifest in various presentations. Risk assessment is essential for predicting the occurrence of future thromboembolism and, therefore, implementing necessary preventive measures before they occur. Different anticoagulants are indicated for different PPCM patient profiles, and careful consideration of their safety profiles in this population is needed.

List of Abbreviations

ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
ART/IVF	Assisted Reproduction Therapy/ In Vitro Fertilization
BMI	Body Mass Index
Bpm	Beat per minute
DCM	Dilated Cardiomyopathy
ECG	Electrocardiogram
ESC	European Society of Cardiology
HCM	Hypertrophic Cardiomyopathy
HES	Hypereosinophilic Syndrome
HR	Heart Rate
LAD	Left Atrium Diameter
LMWH	Low Molecular Weight Heparin
LVAA	Left Ventricular Apical Aneurysm
LVEDD	Left Ventricular End-Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End-Systolic Diameter
LVH	Left Ventricular Hypertrophy
LVNC	Left Ventricular Noncompaction
LVD	Left Ventricular Dysfunction
NOAC	Novel Oral Anticoagulants
OAC	Oral Anticoagulants
OHSS	Ovarian Hyperstimulation Syndrome
PPH	Post-Partum Haemorrhage
PPCM	Peripartum Cardiomyopathy
PTA	Percutaneous Transluminal Angioplasty
RCM	Restrictive Cardiomyopathy
RCOG	Royal College of Obstetricians and Gynecologists
ROS	Reactive Oxygen Species
RV	Right Ventricle
SEC	Spontaneous Echo Contrast
SLE	Systemic Lupus Erythematosus
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTS	Takotsubo Syndrome

UFH	Unfractioned Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

Ethical Clearance

Not Applicable.

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

All authors contributed to the case report writing. Material preparation, data collection and analysis were performed by Muthia Syarifa Yani and Hary Sakti Muliawan. The first draft of the manuscript was written by Muthia Syarifa Yani, and Hary Sakti Muliawan commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Case Reports

Closer Insight through Ventriculo-Arterial Coupling Perspective of Late-recognized Peripartum Cardiomyopathy in The Presence of a Predictor of Non-Recovery: Case Report

Mochamad Rizky Hendiperdana[1]

Abstract

Background: Peripartum Cardiomyopathy (PPCM) is ventricular systolic dysfunction that develops in the last months of pregnancy to several months postpartum. Emerging evidence suggests that PPCM may develop up to 1 year after delivery. This condition is associated with several predictors of non-recovery.

Case Illustration: A 39-year-old woman was admitted with heart failure syndrome. The patient had late-recognized PPCM after an 18-month postpartum period. Echocardiography showed Left Ventricular (LV) dilation and severely reduced Ejection Fraction (EF). The predictor of non-recovery is also present in this case. However, after 5 months of administered Guideline-Directed Medical Treatment (GDMT), the patient developed structural and complete functional reverse remodeling. During the follow-up period, we observed significant improvement in Left Ventricular Ejection Fraction (LVEF) from 23% to 57%, Global Longitudinal Strain (GLS) from –5.2% to –17.5%, Left Atrial Strain (LAS)-reservoir from 8% to 31%, and global work index (GWI) from 516 mmHg% to 1702 mmHg% from myocardial work index analysis.

Conclusions: Several factors have been identified as predictors of non-recovery in PPCM in previous studies, including LVEF <30%, LV dilation, and severe valvular regurgitation. The current scoring system for PPCM recovery, developed by ESC EORP, also predicts 6-month recovery. There was significant improvement in surrogate markers for myocardial systolic function despite of the presence of late-recognized predictors of non-recovery in this case. Hemodynamic phenotype, rather than a single marker measurement, is emerging as a key factor in PPCM prognostication.

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Keywords: Peripartum cardiomyopathy, Hemodynamic phenotype, Ventriculo-arterial coupling, Prognostication, Case report

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Introduction

Peripartum Cardiomyopathy (PPCM) is ventricular systolic dysfunction that develops in the last months of pregnancy to several months postpartum. Emerging evidence suggests that PPCM may develop up to 1 year after delivery. This condition is associated with several predictors of non-recovery. When PPCM is inadequately managed and persists beyond 6 months postpartum, it reduces the potential for recovery and reversibility.[1-4] Although Left Ventricular (LV) function recovery was observed in more than half of the PPCM population,[5] previous studies also describe several factors as poor predictors of LV function recovery in PPCM. These predictors of non-recovery are often linked to baseline severe Left Ventricular Systolic Dysfunction (LVSD) (Left Ventricular Ejection Fraction [LVEF] < 30%), Left Ventricular End-Diastolic Dimension (LVEDD) > 56 mm, Right Ventricular (RV) dysfunction, duration of symptom, national Human Development Index (HDI), QRS duration, and the presence of pre-eclampsia.[4-9]

Case Illustration

A 39-year-old woman presented with progressive shortness of breath, orthopnea, abdominal enlargement, and bilateral pretibial edema (December 2024) (Figure 1 for visual summary). On admission, vital signs were unremarkable. Physical examination was also unremarkable except for the ascites sign. A 12-lead electrocardiography showed sinus rhythm with a QRS duration of 90 ms and no specific abnormality. Chest x-ray revealed cardiac silhouette enlargement with minimal pulmonary congestion sign (Figure 2).

The patient's previous medical record revealed a history of a cesarean section procedure 18 months prior to the patient's recent admission (June 2023), and the patient started to develop clinical symptoms such as dyspnea on effort in September 2023. The patient then started to seek medical attention 2 months after the first clinical symptom (December 2023), but unfortunately, the patient described that the symptom was not well-managed. Then later, the patient developed ascites and was suspected of having liver disease. The patient then lost follow-up for a long period until 2 months prior to recent admission, when the patient developed progressive shortness of breath and abdominal enlargement. Patient denied any fever-like symptoms before the onset of dyspnea and had no family history of cardiac disease.

Blood test examination was unremarkable. Patient has euthyroid profile. Transthoracic echocardiography revealed Right Atrial (RA) dilation with RA area of 26.2 cm^2 (normal < 12 cm^2), LV dilation with LVEDD 58 mm and Left Ventricular End-Diastolic Volume (LVEDV) 157 ml, reduced LVEF of 23%, with LV Global Longitudinal Strain (GLS) value of [-5.2%], reduced RV systolic function (Tricuspid Annular Plane Systolic Excursion [TAPSE] 13 mm) and severe functional tricuspid regurgitation (TR) (Figure 3) (Table 1). Left atrial strain (LAS) assessment also revealed impaired Left Atrial (LA) function (Left Atrial Strain [LAS]-reservoir 8%, LAS-conduit -5%, LAS-contraction -3%) (Figure 4A)(Video 1).

The pressure-strain derived Myocardial Work Indices (MWI) analysis showed severely reduced myocardial systolic performance as follows: Global Work Index (GWI) 516 mmHg%, Global Constructive Work (GCW) 692 mmHg%, Global

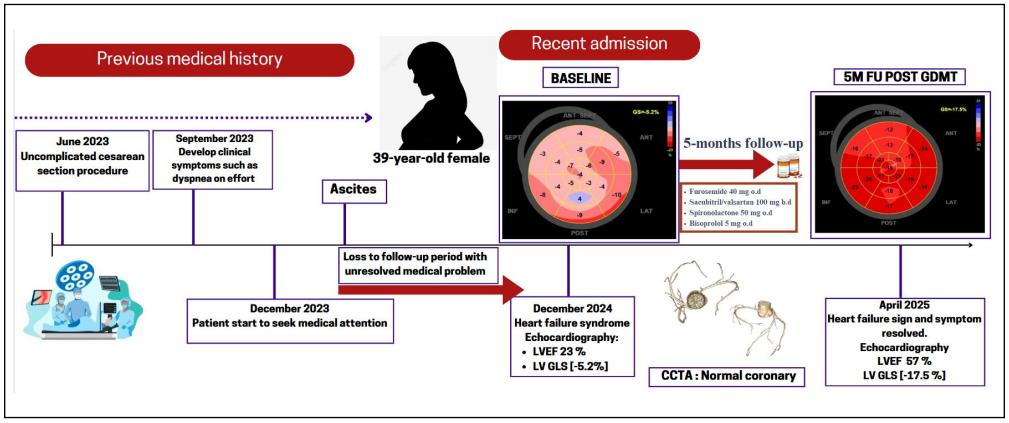

Figure 1. Visual summary of the case. Chronological events and imaging milestone.

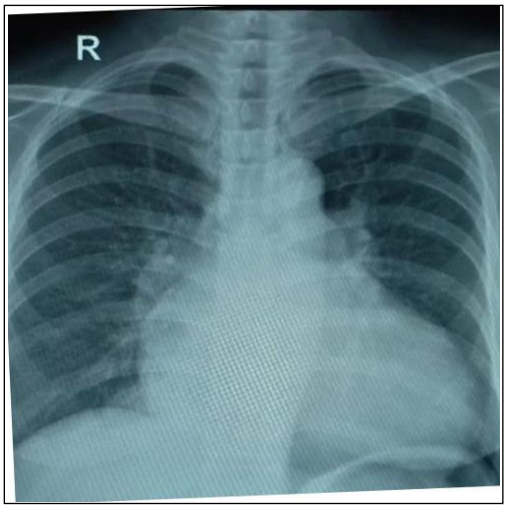

Figure 2. Chest x-ray revealed cardiac silhouette enlargement with minimal pulmonary congestion sign.

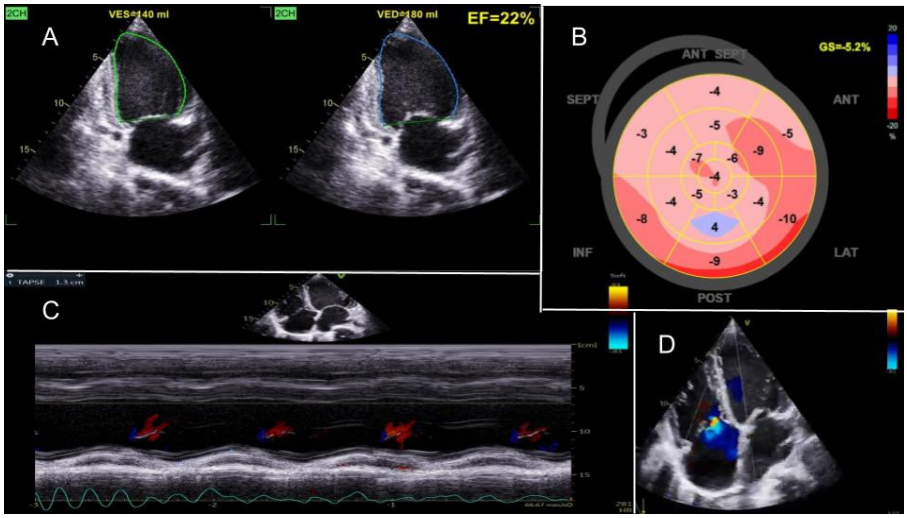

Figure 3. Baseline transthoracic echocardiography revealed: (A) Reduced LV ejection fraction (LVEF) of 23%; (B) Reduced LV GLS value of [-5.2%]; (C) Reduced RV systolic function (TAPSE 13 mm); (D) severe functional TR. LV: left ventricular; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

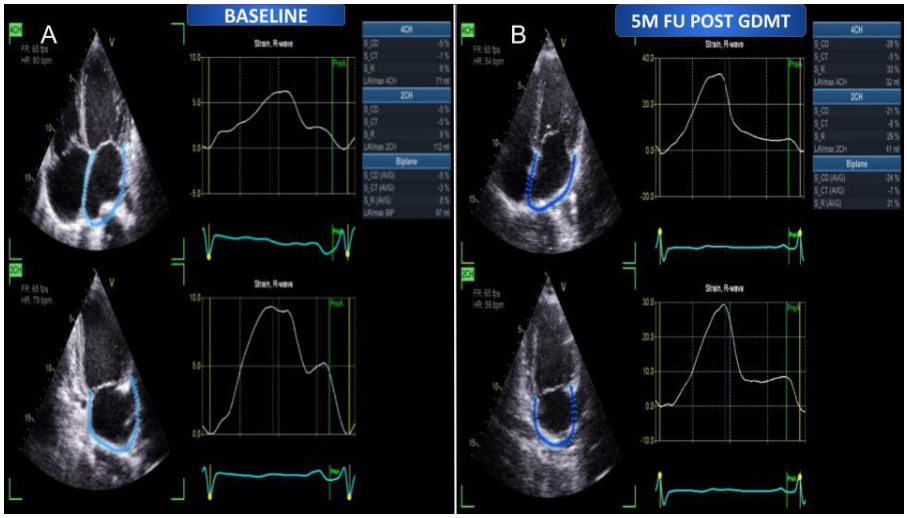

Figure 4. Transthoracic Echocardiography LAS analysis. Left panel: Baseline LAS measurement; Right panel: Post-treatment LAS evaluation showed significant improvement. LAS: left atrial strain.

Table 1. Patient's summary on echocardiographic finding and clinical finding during initial presentation, 3-month post-treatment and 5-months post-treatment.

Parameters	Initial Presentation (December 2024)	3-Month Evaluation (March 2025)	5- Months Evaluation (May 2025)
Echocardiographic Findings (GE Vivid E95) ™			
LVEDV (mL)	157	128	129
LVESV (mL)	121	59	56
LVEDD (mm)	58	54	52
LVEF (%)	23	54	57
TAPSE (mm)	13	18	20
RV S' velocity (cm/s)	7	8	11
Mitral peak E velocity (m/s)	0.56	0.71	0.7
E/e' average	11.47	8.53	9.08
LV averaged GLS (%)	-5.2	-15.8	-17.5
RA area (cm^2) (Normal < 18 cm^2)	26.2	9.9	9.9
Functional TR severity	Severe	Mild	Mild
Clinical Finding			
ECG QRS duration (ms)	90	80	80
Blood pressure (mm/Hg)	137/98	95/60	120/90
Heart rate (beat per minute)	90	60	58

LVEDV: Left Ventricular End-Diastolic Volume; LVESV: Left Ventricular End-Systolic Volume; LVEDD: Left Ventricular End-Diastolic Dimension; LVEF: Left Ventricular Ejection Fraction; TAPSE: Tricuspid Annular Plane Systolic Excursion; RV: Right Ventricle; GLS: Global Longitudinal Strain; LA: Left Atrial; RA: Right Atrial; TR: Tricuspid Regurgitation; ECG: Electrocardiography.

Wasted Work (GWW) 183 mmHg%, Global Work Efficiency (GWE) 77% (Figure 5A) (Table 1). The non-invasive echocardiography-based hemodynamic assessment of Ventriculo-Arterial (VA) coupling showed Elastance arterial (Ea) of 3.51 and Elastance end-systolic (Ees) 1.01 with Ea:Ees ratio 3.47 (Table 2). A Coronary Computed Tomography Angiography (CCTA) showed normal coronary anatomy without stenosis.

The differential diagnosis of the patient's subjective and objective findings can be described as coronary artery disease, myocarditis, autoimmune disorders, thyroid dysfunction, or genetic cardiomyopathies. While coronary stenosis was not found from CCTA, the Coronary Artery Disease (CAD) etiology was unlikely. An euthyroid profile also made thyroid heart disease unlikely. Lastly, the absence of fever and an inflammatory-like syndrome, and the absence of a family history of any cardiac disease, made myocarditis, autoimmune, and genetic cardiomyopathies at least possible. The limitation of Cardiac Magnetic Resonance (CMR) imaging in our case was a lack of a myocardial tissue characterization profile. Therefore, the patient was diagnosed with Heart Failure with reduced Ejection Fraction (HFrEF) due to late-recognized PPCM. Based on these data, the patient was classified as cluster 2 of the hemodynamic PPCM cohort according to Meledin et al.'s study.[4]

Based on these findings, the European Society of Cardiology (ESC) EURObservational Research Programme (EORP) PPCM Recovery Score classified this patient with a recovery score of 4, with a predicted 6-month recovery of 35%. The ESC EORP PPCM Recovery Score elaborated several validated predictors for 6-month recovery, which include baseline LVEF at presentation, either of ≤ 35% or > 35%, LVEDD, national HDI, duration of symptoms, QRS duration, and the presence of pre-eclampsia.[9]

The patient was treated with intravenous loop diuretic for decongestion management along Guideline-Directed Medical Therapy (GDMT) with uptitrated dose to sacubitril/valsartan 100 mg b.i.d., bisoprolol 5 mg o.d., and spironolactone 50 mg o.d. The patient was discharged from hospital admission uneventfully. The patient was then evaluated monthly during outpatient visits.

In five months of outpatient follow-up evaluation (April 2025), the symptoms improved without

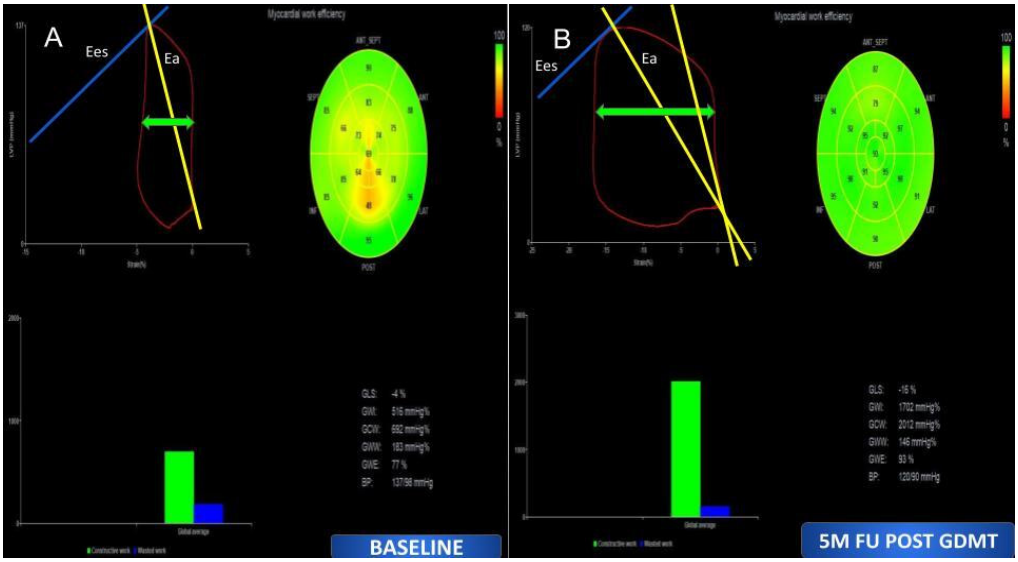

Figure 5. (A) Baseline pressure-strain derived MWI analysis showed severely reduced myocardial systolic performance, which was demonstrated in reduced GWI and GCW. (B) 5-month post-treatment evaluation of MWI showed significant improvement in GWI and GCW. Note that the baseline Ees slope in the PS loop has no difference compared to the post-treatment PS loop. Post-treatment follow-up PS loop resulting in reduced Ea slope angle, which depicts afterload reduction. Green arrow showed increased in stroke work in follow-up compared to the baseline. MWI: myocardial work indices; GWI: global work index; GCW: global constructive work; Ees: end-systolic elastance; Ea: arterial elastance; PS: pressure-strain.

Table 2. Patient's summary on hemodynamic assessment of non-invasive ventriculo-arterial coupling profile at initial presentation and 5-months post-treatment.

Parameters	Initial Presentation (December 2024)	5-Months Evaluation (May 2025)
Echocardiographic Findings (GE Vivid E95) ™		
Systolic blood pressure (mmHg)	137	120
End-systolic pressure (mmHg)	123	108
LV stroke volume (mL)	35	73
LV end-systolic volume (mL)	121	56
Elastance arterial (Ea)	3.51	1.47
Elastance end-systolic (Ees)	1.01	1.92
Ea/Ees ratio	3.47	0.76
GWI (mmHg%)	516	1702
GCW (mmHg%)	692	2012
GWW (mmHg%)	183	146
GWE (%)	77	93

LV: Left ventricular; GWI: Global work index; GCW: Global constructive work; GWW: Global wasted work; GWE: Global work efficiency.

recurrent congestion or ascites. We observed a reduction in RA area and LV volumes (26.2 to 9.9 cm^2 and LVEDV 157 to 128 mL, respectively) (Figure 6) and resolution of TR severity. We also found functional improvement of LV systolic function (LVEF of 57% and LV GLS of [-17.5%]) (Figure 7) (Table 1) with significant LA function improvement (LAS-reservoir 31%, LAS-conduit -24%, LAS-contraction -7%) (Figure 4B). There was a significant improvement in MWI, with GWI 1702 mmHg%, GCW 2012 mmHg%, GWW 146 mmHg%, and GWE 93% (Figure 5B). The non-invasive hemodynamic assessment of VA coupling also showed improvement of Ea:Ees ratio (Table 2) (Video 2).

After complete recovery from imaging criteria was achieved, the patient was advised to use contraception planning, especially non-hormonal contraception like an intrauterine device, to prevent subsequent pregnancy.

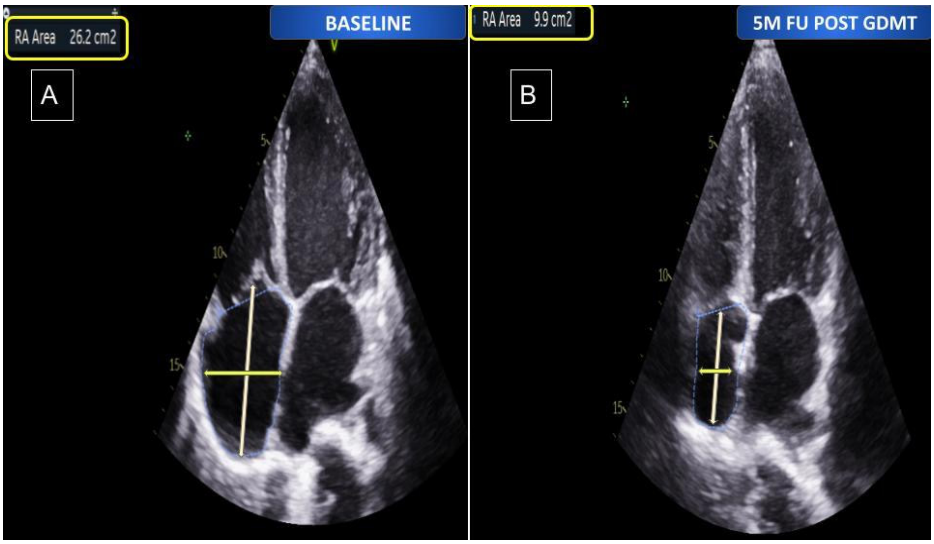

Figure 6. Transthoracic echocardiography. Left panel: Baseline echocardiography revealed RA dilation with RA area of 26.2 cm^2; Right panel: Post-treatment echocardiography evaluation showed a reduction in RA area to 9.9 cm^2. RA: right atrial.

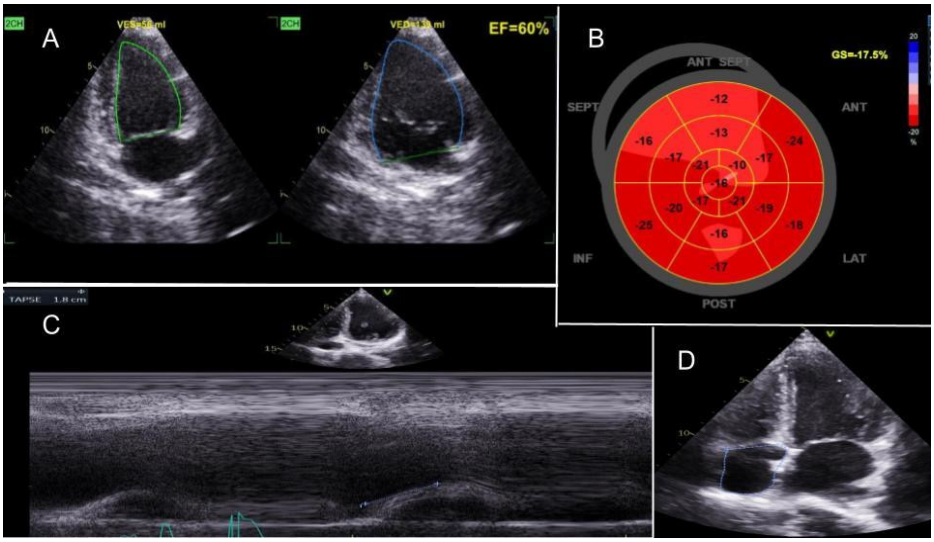

Figure 7. Post-treatment evaluation of transthoracic echocardiography revealed: (A) Improved LV ejection fraction (LVEF) to 57%; (B) Improved LV GLS value to [-17.5 %]; (C) Improved RV systolic function to TAPSE 18 mm; (D) Reduction in RA area. LV: left ventricular; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; RV: right ventricular; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation. RA: right atrial.

Discussion

We presented a young female patient with late-recognized PPCM. Although symptom development commenced during the window period of typical PPCM window period (3 months postpartum), the patient was not recognized or treated for PPCM until 18 months postpartum.

Meledin et al. found that delayed PPCM diagnosis beyond 2 weeks was more common in the non-recovery group than in the recovery group (46.2% vs 20.6%; p = 0.01). Based on this finding, the longer the interval from clinical onset to PPCM diagnosis, the poorer the prognosis for myocardial recovery. In multivariate analysis, baseline LVEF > 35% (HR 6.0; p = 0.008) and baseline LVEDD < 55 mm (HR 4.05; p = 0.029) were the only statistically significant factors associated with a favorable prognosis for recovery.[4]

In addition, ESC EORP PPCM Recovery Score also describes LVEF, LVEDD, and duration of symptoms, which become important prognostic factors.[9] The ESC EORP registry describes LV

recovery that occurred in 46.5% studied population, with a mean change of LVEF of ± 13%. The recovered population has a smaller LA diameter, less frequent RV impairment, and less frequent significant Mitral Regurgitation (MR). Our case showed the presence of a predictor of non-recovery, with 35% prediction of 6-month recovery. Estimating the odds of LV recovery is important for individualizing management decisions and counselling plans.[9] This underlines how exceptional the recovery finding of LVEF in our patient is compared to ESC EORP data. However, our case demonstrated successful Left Heart Reverse Remodeling (LHRR) after 5 months of GDMT, despite long-standing, untreated PPCM, with the presence of a predictor of non-recovery.[1-4] Unfortunately, in some patients, systolic function never completely recovers.[4-5]

More sensitive systolic performance parameters, such as GLS and MWI, did not differ between the recovery and non-recovery groups.[4] This result was contradictory with Sugahara et al.'s finding, which revealed that a reduced GLS (cutoff of [-10.6%]) at baseline was associated with death and persistent LV dysfunction.[10] While our patient also poses poor predictor GLS profile [-5.2%] at initial presentation.

Structural reverse remodeling was observed from a significant reduction in RA size and LV volumes. The functional reverse remodeling is even more significant. The patient showed improvement in LA function, as reflected by increased of all LA strain values, particularly the LAS-reservoir. Moon et al found that in HFrEF patients, improvements of the LAS-reservoir to > 12.5% after GDMT indicate 'complete' LA reverse remodeling, and it is associated with favorable outcomes compared to those whose LAS-reservoir is still < 12.5%.[11]

The LV GLS improvement in our case also poses a favorable prognosis. As described by Moon et al, in HFrEF patients with LV GLS improvement to > [-13%] have a favorable prognosis.[11] As shown in our case, after 5 months of GDMT as recommended in the guidelines,[5,12] the patient achieved significant improvement of LV GLS to [-15.6%]. It appears that traditional predictors of PPCM recovery, such as LVEF, LVEDD, symptom duration, and pre-eclampsia, are insufficient, as our patient demonstrated significant LV recovery despite of low recovery prediction according to the ESC EORP PPCM Recovery score. Hence, emphasizing the need to explore other predictors of recovery.

Meledin et al. proposed a hemodynamic phenotype cluster to predict recovery in PPCM. The study found that cluster 1 hemodynamic phenotype is marked by profound myocardial contractility dysfunction rather than increased afterload. Whereas cluster 2 is marked by relatively more preserved contractility reserve but extremely increased afterload, and cluster 3 is described as having mildly reduced contractility indexes, slightly increased afterload, and preserved cardiac output. Consequently, the recovery rates from clusters 1 to 3 are 12.5%, 78.6%, and 100%, respectively.[4]

We hypothesized that our case hemodynamic phenotype is more closely associated with cluster 2 hemodynamics, with a higher recovery probability, as demonstrated in Figure 5A, whereas the baseline end-systolic elastance (Ees) slope in the Pressure-Strain (PS) loop did not differ compared to the post-treatment PS loop (Figure 5B). Post-treatment follow-up PS loop results in a reduced Ea slope angle, indicating afterload reduction.

In addition to that, as shown in Table 2, non-invasive high Ea and normal Ees reflected very high LV afterload with relatively preserved LV contractility, resulting in VA uncoupling (high Ea:Ees ratio). This non-invasive hemodynamic measurement also showed improved of VA coupling after 5-month follow-up (Ea:Ees ratio 0.76). These data provided clear evidence regarding PPCM recovery in our case, although the presence of a predictor of non-recovery was noted. Hence, our case is consistent with Meledin et al.'s study, which found that hemodynamic phenotype is more predictive of prognosis. However, this inference is hypothesis-generating because invasive data were unavailable.

The usage of sacubitril/valsartan in PPCM, in our case, is extrapolated from GDMT for Dilated Cardiomyopathy (DCM) and HFrEF. The evidence of sacubitril/valsartan usage in PPCM case is remains limited but supportive.[5,13-17] This report could be additional real-world clinical experience data of sacubitril/valsartan usage in PPCM patients. The administration of GDMT in our case was continued for 6 months after complete recovery was achieved. In non-recovery PPCM or persistent LV dysfunction, the GDMT is expected to continue indefinitely.[1] Bromocriptine is deferred in our case, considering the late-recognized origin in this case.

The optimal GDMT duration after LV recovery is still unknown, while evidence shows the latent risk of late deterioration of LV dysfunction without the presence of subsequent pregnancy. Therefore, continuing heart failure GDMT is rational in this case. However, if GDMT is intended to be

discontinued; the stepwise strategy should be kept in mind. GDMT weaning should be accompanied by serial echocardiographic monitoring (every 3 to 6 months). Evaluation of LV function is recommended after discontinuation of GDMT, followed by annual echocardiographic assessment.[1]

It is recommended that the patient be advised concerning contraception. In our case, the multidisciplinary team considered avoiding estrogen-releasing contraceptives due to thromboembolism risk. In recovered PPCM, the subsequent pregnancy still carries the recurrence risk with a ± 20% relapse rate. However, in a non-recovered woman with persistent LV dysfunction, the risk of a subsequent pregnancy outweighs any risk associated with contraception (50% relapse rate and increased mortality for subsequent pregnancy). Hence, women should be encouraged to select their preferred contraceptive method.[1]

Conclusion

This case reported 'complete' LHRR in the setting of late-recognized PPCM with the presence of a predictor of non-recovery, with a 6-month LV recovery prediction of 35 % according to the ESC EORP PPCM Recovery Score. Highlighting the importance and efficacy of optimal GDMT for HFrEF in facilitating complete cardiac function recovery in the presence of a predictor of non-recovery PPCM. Finally, this case underscored the use of hemodynamic phenotyping and non-conventional echocardiographic parameters to evaluate a more sensitive surrogate marker of myocardial recovery for clinical decision-making.

List of Abbreviations

CAD	Coronary Artery Disease
CCTA	Coronary Computed Tomography Angiography
CMR	Cardiac Magnetic Resonance
DCM	Dilated Cardiomyopathy
Ea	Elastance arterial
Ees	Elastance end-systolic
ESC	European Society of Cardiology
GCW	Global Constructive Work
GDMT	Guideline-Directed Medical Treatment
GLS	Global Longitudinal Strain
GWE	Global Work Efficiency
GWI	Global Work Index
GWW	Global Wasted Work
HDI	Human Development Index
HFrEF	Heart Failure with Reduced Ejection Fraction
LAS	Left Atrial Strain
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
LVEDD	Left Ventricular End-Diastolic Dimension
LVEDV	Left Ventricular End-Diastolic Volume
MWI	Myocardial Work Index
PPCM	Peripartum Cardiomyopathy
PS	Pressure-Strain
RA	Right Atrial
RV	Right Ventricular
TAPSE	Tricuspid Annular Plane Systolic Excursion
VA	Ventriculo-Arterial

Ethical Clearance

Patient consent for publication and institutional approval as per journal policy were obtained.

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Conflict of Interest

The author stated no conflict of interest and nothing to disclose.

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The author declares that no artificial intelligence (AI) tools were used in the writing, analysis, or preparation of this manuscript.

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Case Reports

The Forgotten Spongy Myocardium: Clinical Trajectory of Left Ventricular Noncompaction Cardiomyopathy in an Asymptomatic Adult

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Abstract

Background: Left Ventricular Noncompaction (LVNC) is a rare cardiomyopathy characterized by a thin compacted epicardial layer and an extensive noncompacted endocardial layer with prominent trabeculations and deep intertrabecular recesses that communicate with the Left Ventricular (LV) cavity. The classic triad of complications includes chronic heart failure, ventricular arrhythmias, and systemic embolic events. At present, evidence-based management guidelines remain limited.

Case Illustration: We report a 42-year-old man with LVNC, initially detected as an incidental Left Bundle Branch Block (LBBB) on Electrocardiogram (ECG) during a routine medical checkup. Although he remained asymptomatic, LV Ejection Fraction (LVEF) progressively declined, accompanied by rising N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) levels. Coronary artery disease was excluded by coronary computed tomography angiography. Given worsening LV systolic function over 2 years, Cardiac Magnetic Resonance (CMR) demonstrated an LVNC phenotype consistent with cardiomyopathy. Guideline-Directed Medical Therapy (GDMT) for heart failure was initiated, along with oral anticoagulation for primary prevention of LV thrombus. After medication optimization, LVEF improved markedly, and NT-proBNP normalized.

Conclusions: This case illustrates the value of comprehensive evaluation and multimodality imaging in patients with unexplained LBBB, even when asymptomatic. Early diagnosis, phenotype-guided treatment, and longitudinal surveillance may help prevent clinical progression and future heart-failure, arrhythmic, or thromboembolic complications.

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Keywords: Isolated Noncompaction of the Ventricular Myocardium, Cardiomyopathies, Bundle-Branch Block, Magnetic Resonance Imaging, Heart Failure

Introduction

Left Ventricular Noncompaction (LVNC) is a rare cardiomyopathy characterized by prominent trabeculations and deep intertrabecular recesses, producing a spongy myocardial appearance.[1] The American Heart Association (AHA) classifies LVNC as a primary genetic cardiomyopathy, whereas the European Society of Cardiology (ESC) considers it an unclassified cardiomyopathy.[2-3] LVNC predominantly involves the left ventricle and features a two-layered myocardium, with a thick noncompacted trabecular layer over a thinner compacted layer. It can present at any age, including mid-life, but reported prevalence in imaging series is low (approximately 0.01-0.26%), and it is identified more often in men, potentially due in part to under-recognition of asymptomatic cases.[4-5] Patients with LVNC are at increased risk of progression to heart failure, life-threatening ventricular arrhythmias, and thromboembolic events related to intracardiac thrombus formation.[6]

Diagnosing LVNC can be difficult because clinical presentation ranges from incidental findings to advanced heart failure, and Electrocardiography (ECG) findings are non-specific.[7-8] Common ECG features include increased QRS complex voltage, Left Bundle Branch Block (LBBB), and ST-T wave abnormalities. Arrhy thmias are also frequent.[9-10] LVNC is typically suspected on Transthoracic Echocardiography (TTE) and can be confirmed by Cardiac Magnetic Resonance imaging (CMR). On echocardiography, LVNC is classically recognized by a two-layered myocardium, consisting of a thin compacted epicardial layer and a thicker noncompacted endocardial layer with prominent trabeculations and deep intertrabecular recesses communicating with the LV cavity. Established echocardiographic frameworks include the Jenni, Chin, and Stöllberger criteria, which assess compacted and noncompacted myocardial layers, trabeculation morphology, and intertrabecular recesses. On CMR, prominent trabeculations commonly involve the apical and mid-lateral left ventricular (LV) segments, and a maximal Noncompacted-to-Compacted (NC/C) myocardial thickness ratio >2.3 at end-diastole fulfills the Petersen criterion.[11] While echocardiography remains the first-line, widely accessible imaging modality, CMR provides complementary value through higher spatial resolution and more reproducible quantification of myocardial layers, particularly when echocardiographic windows are limited or diagnostic uncertainty persists.[12]

In addition to diagnostic challenges, evidence guiding treatment strategies for LVNC remains limited, and current approaches are largely individualized. Management typically focuses on associated clinical manifestations such as heart failure, atrial fibrillation, thromboembolism, and arrhythmias.[3,13] Prognosis is highly variable and is influenced by the timing of detection and the development of complications, including ventricular arrhythmias, heart failure, and thromboembolic events. In adults, mortality rates of up to 50% within 6 years after diagnosis have been reported.[6]

In Indonesia, the relatively limited availability of magnetic resonance imaging, together with documented barriers to clinical CMR implementation in Asia and other low- and middle-income settings, likely contributes to delayed diagnosis and under-recognition of cardiomyopathies that require advanced imaging, including LVNC.[14-15] To our knowledge, published case reports describing the clinical course of LVNC in Indonesia remain limited. Herein, we present an asymptomatic adult patient with LVNC who developed LV systolic dysfunction and complete LBBB.

Case Illustration

A 42-year-old Chinese man with long-standing hypertension and metabolic syndrome presented to our outpatient clinic in October 2024 for further evaluation of previously identified complete LBBB and reduced LV Ejection Fraction (LVEF). He remained asymptomatic during activities of daily living and denied exertional dyspnea, chest pain, palpitations, syncope, presyncope, orthopnea, paroxysmal nocturnal dyspnea, or peripheral edema. He denied tobacco or alcohol use and reported no known family history of cardiomyopathy, heart failure, sudden cardiac death, unexplained syncope, arrhythmia, device implantation, or premature cardiovascular disease. Vital signs and physical examination were unremarkable.

The initial abnormality was incidentally detected in March 2021, when a routine medical checkup showed complete LBBB on ECG (Figure 1). Coronary artery disease was excluded by Coronary Computed Tomography Angiography (CCTA). Standard laboratory tests and Transthoracic Echocardiography (TTE) were unremarkable, with preserved LVEF (62%). Over time, LVEF declined to 46% by October 2023, without evidence of LV thrombus, and he remained asymptomatic. No specific therapy was initiated at that time.

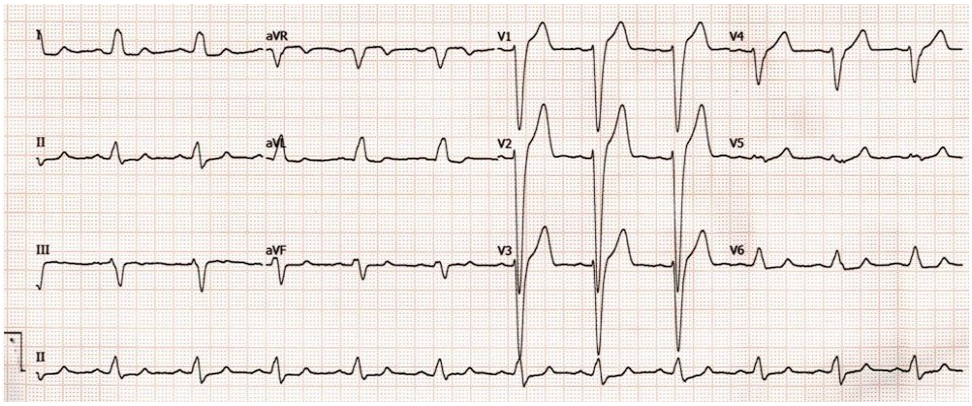

Figure 1. ECG showing complete LBBB.

At presentation in October 2024, repeat TTE showed a markedly reduced LVEF of 25% with global LV hypokinesia (Figure 2), accompanied by an elevated N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) level of 531 pg/mL. Repeat CCTA during the same period demonstrated only mild, non-obstructive coronary plaque. CMR revealed an LVNC phenotype with a maximal NC/C ratio of 3.5, fulfilling the Petersen criterion (>2.3), together with global hypokinesia and no late gadolinium enhancement or evidence of fibrosis or myocardial inflammation.

Guideline-Directed Medical Therapy (GDMT) was initiated, consisting of candesartan 16 mg once daily, bisoprolol 2.5 mg twice daily, spironolactone 25 mg once daily, dapagliflozin 10 mg once daily, rosuvastatin 20 mg once daily, and metformin 1,000 mg once daily. Given the markedly reduced LVEF and extensive trabeculation, low-dose edoxaban (30 mg once daily) was prescribed for primary prevention of thromboembolism. Candesartan was subsequently switched to sacubitril/valsartan 100 mg twice daily to promote LV reverse remodeling.

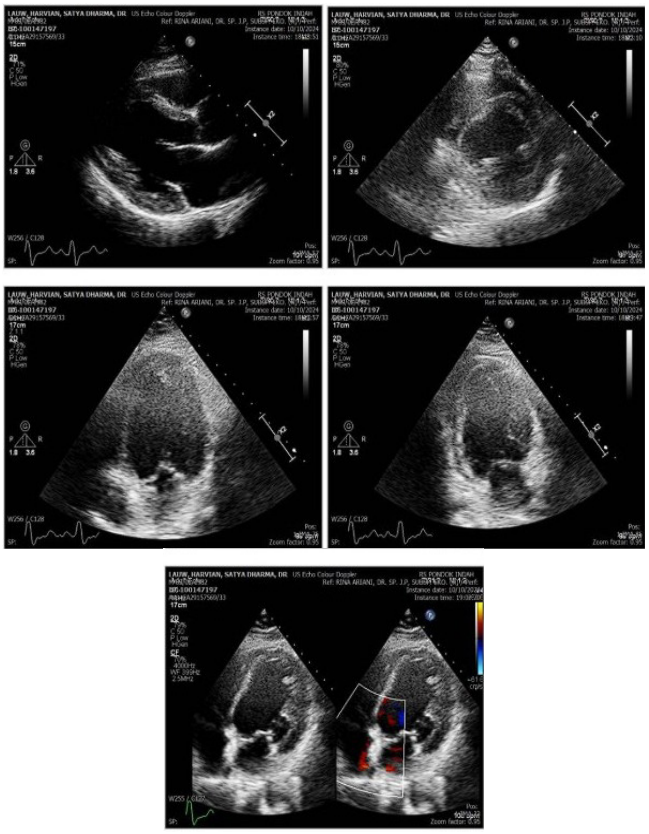

Figure 2. Initial TTE in October 2024.

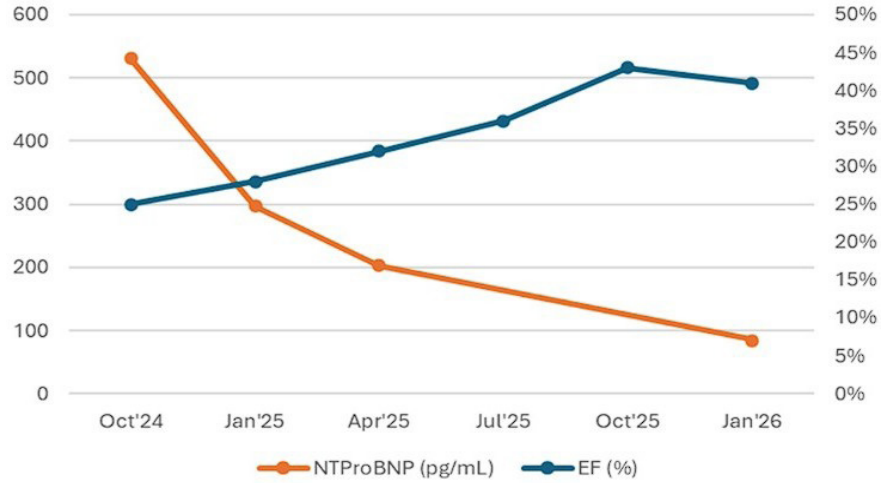

Figure 3. Trends in LVEF and NT-proBNP during GDMT.

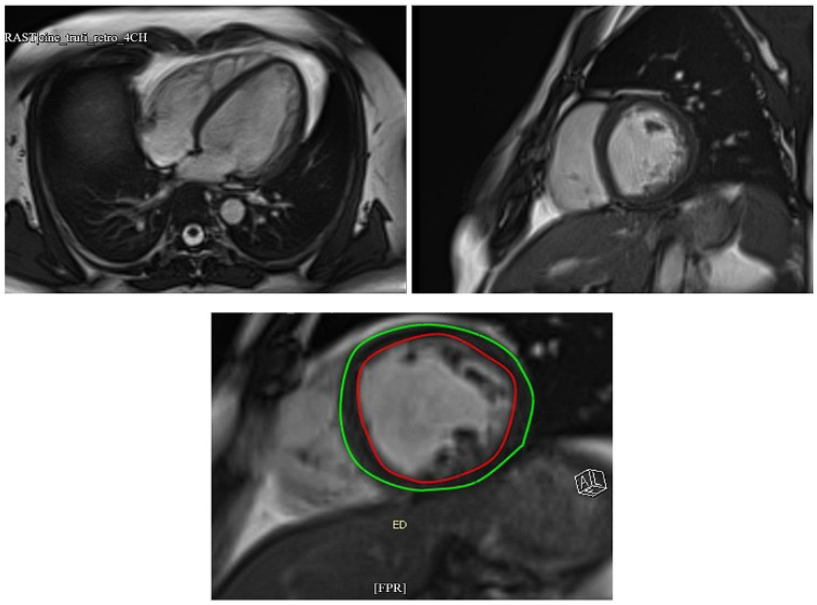

Figure 4. A follow-up CMR in October 2025 showed improved LV systolic function following GDMT optimization.

Guideline-Directed Medical Therapy (GDMT) was initiated, consisting of candesartan 16 mg once daily, bisoprolol 2.5 mg twice daily, spironolactone 25 mg once daily, dapagliflozin 10 mg once daily, rosuvastatin 20 mg once daily, and metformin 1,000 mg once daily. Given the markedly reduced LVEF and extensive trabeculation, low-dose edoxaban (30 mg once daily) was prescribed for primary prevention of thromboembolism. Candesartan was subsequently switched to sacubitril/valsartan 100 mg twice daily to promote LV reverse remodeling.

Over the subsequent 12 months, the patient remained clinically asymptomatic, with progressive improvement in LVEF and a decline in NT-proBNP levels (Figure 3). Serial ECGs and 24-hour Holter monitoring showed no significant arrhythmias. Repeat CMR in October 2025 (Figure 4) demonstrated partial reverse remodeling, with LVEF of 43%, an NC/C ratio of 3.3, and no LV thrombus. Cardiopulmonary exercise testing showed adequate functional capacity, with a peak VO_2 of 19.9 mL/kg/min and a normal hemodynamic response to exercise. Given the improvement in LVEF and persistent absence of symptoms, GDMT was continued, and consideration of cardiac resynchronization therapy was deferred.

Discussion

LVNC describes a myocardial phenotype characterized by prominent trabeculations and deep intertrabecular recesses, and may be associated with LV dysfunction, arrhythmias, and thromboembolic complications.[16] LVNC remains diagnostically challenging because reported prevalence varies by population, imaging modality, and diagnostic criteria. Meta-analyses suggest higher prevalence estimates when CMR criteria are applied, raising concern for overdiagnosis of physiological hypertrabeculation and potential overtreatment.[17] Clinical features that prompt careful evaluation are therefore important. Although ECG abnormalities are common and often non-specific, observational data indicate that intraventricular conduction disturbances, including LBBB, are frequently encountered in LVNC cohorts.[18] In our patient, incidentally detected complete LBBB preceded recognition of LV systolic impairment, and diagnosis was delayed until serial imaging showed progressive LVEF decline and CMR confirmed LVNC.

CMR was pivotal for confirmation and risk stratification. CMR-based morphologic thresholds, such as an NC/C ratio >2.3 at end-diastole (Petersen criterion), are widely used, with the understanding that no single criterion is definitive and that imaging findings require clinical correlation. Other CMR-based approaches, including Jacquier, Stacey, Captur/fractal analysis, and indexed non-compacted mass criteria, have also been proposed; however, these criteria vary in diagnostic yield and are not uniformly applied in routine clinical reporting.[12] In our patient, CMR demonstrated marked trabeculation (NC/C 3.5) and global hypokinesia, without late gadolinium enhancement or evidence of myocardial inflammation. Late gadolinium enhancement, as a surrogate for myocardial fibrosis, has prognostic relevance across cardiomyopathies and in LVNC. Meta-analysis data in LVNC cohorts have associated late gadolinium enhancement with a higher risk of major adverse cardiovascular events, supporting its role as a clinically useful risk marker.[19] Accordingly, absence of these CMR features may be favorable, although reduced LVEF remains a key determinant of outcome in LVNC.[20-21]

In the absence of robust randomized evidence and LVNC-specific therapeutic algorithms, management is typically individualized and guided by the dominant clinical phenotype (heart failure, arrhythmia burden, and thromboembolic risk).[22] In patients with LV systolic dysfunction, GDMT for heart failure with reduced ejection fraction remains the cornerstone, including renin-angiotensin system inhibition, beta-blocker, mineralocorticoid receptor antagonist, and Sodium-Glucose Cotransporter-2 (SGLT2) inhibitor.[2,10,23] The patient in this report received comprehensive GDMT (Angiotensin Receptor-Neprilysin Inhibitor [ARNI], beta-blocker, mineralocorticoid receptor antagonist, and SGLT2 inhibitor), with objective improvement in LVEF and NT-proBNP over 12 months and preserved functional status. Case-based reports and reviews suggest that ARNI therapy may be associated with reverse remodeling in LVNC, including improvement in LVEF and ventricular dimensions.[7] In parallel, a prospective cohort of 30 LVNC patients on stable GDMT reported that addition of an SGLT2 inhibitor was associated with LV reverse remodeling, improved hemodynamic indices, and NT-proBNP reduction at 12 months, particularly in less advanced disease.[24] Taken together, these observations support early initiation and careful optimization of GDMT in patients with LVNC and LV systolic dysfunction.

Device therapy decisions in LVNC should follow standard indications based on LVEF, symptoms, and electrical or mechanical dyssynchrony, rather than trabeculation morphology alone.[2,10,23] Persistent LBBB raised consideration of resynchronization strategies; however, because LVEF improved with GDMT and no sustained ventricular arrhythmias were documented, cardiac resynchronization therapy and implantable cardioverter-defibrillator implantation were deferred. Continued rhythm surveillance remains reasonable, given the association of LVNC with atrial and ventricular arrhythmias and the potential for late arrhythmic events.[16]

Thromboembolism prevention remains a key management question in LVNC and is an important consideration in this case. Thromboembolic events occur in LVNC, and systematic review data suggest a higher risk in the presence of atrial fibrillation and/or LV systolic dysfunction.[25] In the absence of atrial fibrillation, intracardiac thrombus, or prior embolic events, prophylactic anticoagulation is not established by randomized evidence. Nonetheless, expert opinion and observational experience support considering anticoagulation in selected higher-risk LVNC phenotypes, particularly in patients with markedly reduced LVEF, after individualized bleeding-risk assessment.[9] Therefore, reduced-dose edoxaban in this case should be interpreted as a risk-mitigation strategy in the setting of severe systolic dysfunction and extensive trabeculation, rather than a standard-of-care approach.

Several limitations should be acknowledged. First, LVNC diagnostic criteria are heterogeneous and overlap with physiological trabeculation; in this patient, the diagnosis was supported by concordant imaging findings and a trajectory of progressive LV dysfunction. Echocardiographic assessment of quantitative LVNC indices, including the Jenni, Chin, and Stöllberger criteria, was limited by suboptimal acoustic windows, which precluded reliable retrospective measurement of myocardial layer thickness and trabeculation ratios. Therefore, TTE was used primarily for serial assessment of LV systolic function, while LVNC morphology was quantified and diagnostically supported by CMR using the Petersen criterion.[12,17] Second, the mechanism underlying LV systolic dysfunction remains uncertain. Obstructive coronary artery disease was not supported by CCTA, and CMR showed no late gadolinium enhancement, myocardial inflammation, or scar, making ischemic, inflammatory, or scar-mediated cardiomyopathy less likely. Because complete LBBB preceded overt systolic dysfunction, LBBB-related dyssynchrony may have contributed, although LVNC-associated cardiomyopathy remains a plausible primary substrate.[26] Although prior TTE documented preserved LVEF in 2021, no earlier CMR or LVNC-focused echocardiographic assessment was available; therefore, we could not determine whether the noncompaction morphology was already present, became more apparent with LV remodeling, or was previously under-recognized. Third, genetic testing and structured family evaluation were not performed. This is relevant because LVNC may show familial clustering, with prior studies reporting cardiomyopathy among relatives in approximately 17% to 50% of affected patients.[27] Accordingly, genetic counseling and clinical screening of first-degree relatives, including focused history, ECG, and echocardiography, should be considered, particularly because affected relatives may be asymptomatic.[3,16] Longer follow-up is needed to confirm the durability of reverse remodeling, arrhythmia-free status, and thromboembolic risk over time.

Conclusion

This case illustrates that otherwise unexplained complete LBBB may serve as an early clinical clue to an underlying cardiomyopathy, such as LVNC, before overt clinical manifestations develop. Timely, comprehensive evaluation, including multimodal imaging, is important for early detection and diagnostic confirmation, enabling earlier initiation of appropriate therapy and potentially improving clinical outcomes. Although evidence for LVNC-specific therapy remains limited, phenotype-guided management with contemporary GDMT was associated with substantial improvement in LVEF and NT-proBNP in this patient. Continued follow-up remains important to monitor the durability of reverse remodeling and to reduce the risk of future heart-failure progression, ventricular arrhythmias, and thromboembolic complications.

List of Abbreviations

AHA	American Heart Association
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
CCTA	Coronary Computed Tomography Angiography
CMR	Cardiac Magnetic Resonance
ECG	Electrocardiogram
ESC	European Society of Cardiology
GDMT	Guideline-Directed Medical Therapy
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVNC	Left Ventricular Noncompaction
MeSH	Medical Subject Headings
NC/C	Noncompacted-to-compacted myocardial thickness ratio
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
SGLT2	Sodium-Glucose Cotransporter-2
TTE	Transthoracic Echocardiography
VO_2	Oxygen uptake

Ethical Clearance

Ethics committee or institutional review board approval was not required for publication of this single case report in accordance with local institutional policy. The report was prepared using anonymized clinical information. Written informed consent for publication of the clinical details and any accompanying images was obtained from the patient. Identifying information has been removed to protect privacy

Publication Approval

The corresponding author confirms that all authors reviewed and approved the final version of the manuscript and consent to its submission. The

work is original and is not under consideration by another journal, nor has it been published previously, in whole or in part.

Authors Contributions

SSI, JWH, and HSD collected and curated the clinical data, performed the literature review, and prepared the first draft. LPS contributed to the clinical management and helped frame the clinical narrative. DYG provided electrophysiology and ECG/Holter interpretation. LPS and DYG provided final revisions and critical intellectual input. All authors contributed to the manuscript revision, approved the final version, and agreed to be accountable for the accuracy and integrity of the work.

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The authors have no acknowledgements to declare.

Conflict of Interest

All authors declare that they have no competing interests (financial or non-financial) relevant to this work.

Availability of Data and Materials

All data relevant to this case are included in the manuscript. Additional de-identified information may be made available by the corresponding author upon reasonable request, subject to patient consent and institutional/privacy restrictions.

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Generative AI and AI-Assisted Technologies in the Writing Process

Generative AI (ChatGPT 5.4 Pro, OpenAI) was used only to improve language, grammar, and clarity. The tool was not used to generate or modify clinical data, analyses, interpretations, or conclusions, and no identifiable patient information was entered. All authors review and take full responsibility for the final content.

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Case Reports

Benign Prostate Hyperplasia (BPH) – Induced Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): A Rare Precipitant of Acute Decompensated Heart Failure

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Abstract

Background: In Acute Decompensation of Heart Failure (ADHF), precipitating factors must be promptly identified and treated. Urinary retention is rarely recognized as a cause of ADHF. Here, we presented a case of Benign Prostate Hyperplasia (BPH) with urinary retention inducing SIADH, which precipitated a recurrent episode of decompensated heart failure.

Case Illustration: a 73-year-old male with a history of hypertension, admitted with signs and symptoms of urinary obstruction. He was scheduled for Transurethral Resection of the Prostate (TURP), but the procedure was delayed due to hyponatremia (serum sodium 119 mmol/l). But while correcting hyponatremia with saline solution, the patient developed worsening dyspnea along with rhonchi and desaturation, which suggested acute heart failure. Chest X-rays showed pulmonary congestion and possible infection; echocardiography indicated concentric LV hypertrophy with normal ejection fraction (LVEF 60%), consistent with HFpEF. He was admitted to the ICU for monitoring, on IV diuretics, fluid restriction, and antibiotics. Intravenous furosemide and tolvaptan improved his symptoms and sodium, leading to ward transfer. Work-up for the hyponatremia showed high urinary sodium without any other cause, supporting the SIADH diagnosis. However, despite treatment and initial improvement, the patient's serum sodium remained below normal (approximately 124 mmol/l) for over a week. He requests removal of the Foley catheter because he already feels much better. However, three days later, he suddenly had severe dyspnea with oxygen saturation dropping to 76% on a nasal cannula and only rising to 89% on 15 liters of oxygen at a non-rebreather mask. He was urgently transferred back into the ICU. Bedside echocardiography showed another episode of decompensated heart failure. Laboratory results showed worsening of hyponatremia (121 mmol/L). The Foley catheter was reinserted because there was evidence of obstruction and inadequate diuresis. The furosemide IV and tolvaptan were continued. The patient's condition and respiratory status improved, with SpO 2 94-97% on 10 L/min via a simple face mask.

Conclusions: Benign Prostatic Hyperplasia (BPH), even in rare instances, can induce SIADH, resulting in renal water retention and potentially causing acute decompensated heart failure.

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Keywords: Benign Prostate Hyperplasia, SIADH, Acute Heart Failure, HFpEF

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Introduction

Acute decompensation in patients with previously stable chronic heart failure is common and associated with substantial morbidity.[5] Causes of such decompensation episodes need to be identified and treated promptly.[5-7] While typical precipitating factors are well described, urinary retention is rarely recognized as a cause of heart failure decompensation.[6,8-9] Benign Prostatic Hyperplasia (BPH) with urinary retention can act as a neurogenic trigger for the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), which can precipitate Acute Decompensated Heart Failure (ADHF), particularly in vulnerable patients. [1-2] We present a rare case of BPH-induced SIADH that resulted in severe, refractory hyponatremia, leading to recurrent, life-threatening episodes of ADHF in a patient with Heart Failure with preserved Ejection Fraction (HFpEF).

Case Illustration

A 73-year-old male with a history of hypertension and BPH was admitted for an elective urological procedure to address Lower Urinary Tract Symptoms (LUTS) resulting from prostatic hyperplasia. He first came to the urology department in January 2025 and has been diagnosed with BPH since then, with an estimated prostate volume of 32.6 cm^3, accompanied by calcification intra-prostate. He had a history of difficulty in urinating for 3 days before hospital admission. He reported sensation to urinate but was only able to produce a small amount with a persistent feeling of residual urine. Due to this symptom, he visited another hospital and got a DC insertion with urinary production of about 500 ml after DC placement. After that, he referred to our hospital and planned to have surgery for his prostate. His vital signs were stable, with blood pressure 151/95 mmHg, heart rate 100 beats per minute, respiratory rate 20 breaths per minute, oxygen saturation 95% on room air, and body temperature 37.5°C. The procedure was subsequently postponed following admission when routine preoperative laboratory investigations revealed severe hyponatremia, with a serum sodium level of 119 mmol/l. Other laboratory and physical findings were normal.

During the initial hours of electrolyte correction with hypertonic and isotonic saline (3% NaCl at 20 mL/h, administered abruptly and concurrently with 0.9% Nacl at 40 mL/h), the patient suddenly developed dyspnea and orthopnea. Blood pressure was 161/113 mmHg, heart rate was 100 beats per minute, and oxygen saturation was 83% on nasal cannula, improving to 96% with 10 L/min of oxygen delivered via a simple face mask. Bilateral rales were noted on physical examination. Clinical assessment and imaging strongly suggested ADHF. Chest X-ray (CXR) confirmed pulmonary congestion and showed findings suggestive of pulmonary infection. Transthoracic Echocardiography (TTE) demonstrated concentric left ventricular hypertrophy with preserved systolic function (Left Ventricular Ejection Fraction [LVEF] 60%), normal global kinetic wall motion, and normal valvular function, consistent with HFpEF. The Inferior Vena Cava (IVC) diameter (9/12 mmHg) and an estimated Right Arterial Pressure (eRAP) of 8 – 10 mmHg indicated a mild elevation; however, the predominant clinical manifestation was acute pulmonary oedema. The patient was admitted to the intensive care unit for close monitoring and standby for intubation if necessary. He also received intravenous diuretics, fluid restriction, and antibiotics for pneumonia.

The initial treatment of ADHF involved administering intravenous Furosemide and the vasopressin V2 receptor antagonist, Tolvaptan. The patient's dyspnea improved, and his serum sodium levels rose slightly, so he was stepped down to the ward. An investigation into the ongoing hyponatremia showed high urinary sodium (Table 1) without any other appropriate cause, strengthening the evidence of SIADH.

Table 1. Urine electrolyte panel.

Examination	Urine Electrolyte Panel (Na, K, Cl)		
Volume Urine / 24 Hours	3600	—	mL/24 hours
Sodium (Na) – Urine	310	54–150	mEq/L
Potassium (K) – Urine	58	25–100	mEq/24 hours
Chloride (Cl) – Urine	317	85–170	mEq/24 hours

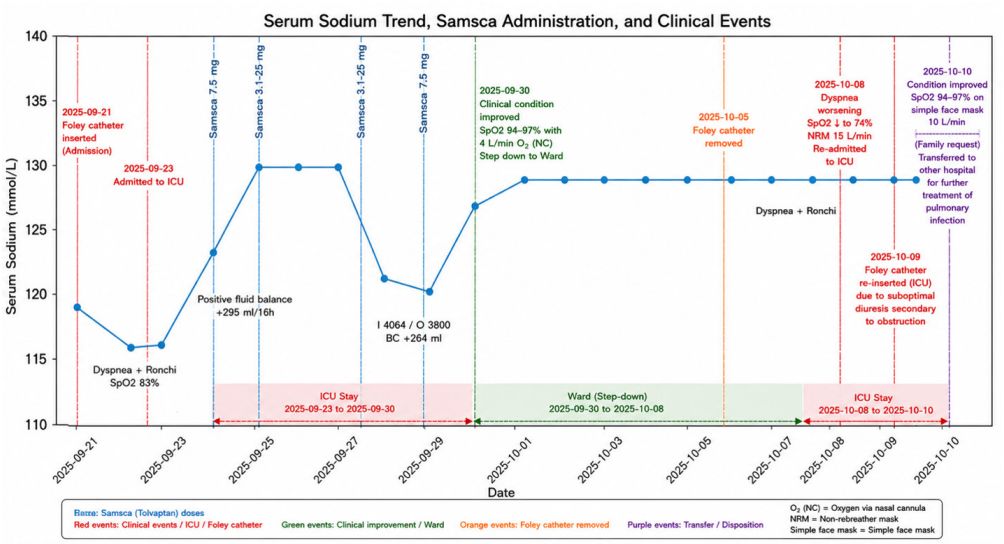

Figure 1. Temporal relationship between serum sodium levels, tolvaptan administration, and clinical events.

Despite appropriate medical treatment and an initially favorable response, the patient's serum sodium remained below normal, around 124 mmol/L, for more than one week of hospitalization. The patient clinically improved and requested removal of the Foley catheter on the 5th of October. On the fourteenth day, however, he suddenly experienced a severe recurrence of dyspnea, accompanied by hypoxemia, with oxygen saturation falling to 76% on a nasal cannula and rising only to 89% with a non-rebreather mask at 15 L/min. He was urgently transferred again to the ICU for stabilization. Bedside echocardiography revealed an IVC diameter of 13/17 mmHg with an estimated eRAP of 8-10 mmH_2O. Laboratory tests showed worsening hyponatremia with 121 mmol/L. Hypertonic 3% Nacl was continued intermittently along with intravenous furosemide. The Foley catheter was reinserted, and this time we ensured it remained in place to prevent urinary retention and maintain continuous urinary monitoring.

In Figure 1, the graph shows the serial trend of serum sodium levels during hospitalization, along with the timing and dosage of tolvaptan (Samsca) administration and major clinical events. The patient was admitted on September 21, 2025, with signs and symptoms of urinary obstruction and was scheduled for Transurethral Resection of the Prostate (TURP). A Foley catheter was inserted at admission. While correcting hyponatremia with normal saline and 3% NaCl, the patient developed worsening dyspnea, ronchi, and severe desaturation to SpO_2 83% on September 23, 2025, which led to ICU admission. After starting tolvaptan, serum sodium gradually rose from 116–119 mmol/L to 130 mmol/L between September 25–27, 2025, though intermittent positive fluid balance persisted. On September 30, 2025, the patient showed clinical improvement, with SpO_2 94–97% on 4 L/min oxygen via nasal cannula, and was transferred out of the ICU. Following Foley catheter removal on October 5, 2025, serum sodium remained relatively stable at approximately 129 mmol/L, but ongoing dyspnea and rhonchi indicated continued congestion despite biochemical improvements. On October 8, 2025, the patient's respiratory condition worsened, with severe desaturation to 74%, requiring a non-rebreather mask oxygen at 15 L/min and ICU re-admission. On October 9, 2025, Foley catheter re-insertion was performed due to suspected urinary obstruction and insufficient diuresis. By October 10, 2025, respiratory status had improved, with SpO_2 94–97% on a simple face mask at 10 L/min; however, the patient was ultimately transferred to another hospital for further treatment of a pulmonary infection at the family's request.

Discussion

Chronic heart failure leads to frequent hospitalizations and increasing healthcare costs.[5] Effective management requires not only diagnosing heart failure but also identifying and treating the factors that precipitate clinical deterioration in both outpatient and inpatient settings.[5-7] In cases of decompensated chronic heart failure, determining the trigger of the

episode is essential, regardless of whether systolic or diastolic dysfunction is present.[9]

Common precipitating factors for heart failure decompensation include medication non-adherence, myocardial ischemia, cardiac arrhythmias, sepsis, uncontrolled hypertension, and suboptimal medical therapy before admission.[9] In contrast, urinary retention has not been well described in the literature as a trigger for decompensated heart failure.[1,8-9] Our case report aims to highlight this connection, where SIADH caused by Benign Prostatic Hypertrophy was identified as the cause of urinary retention, which in turn led to refractory decompensated heart failure.

We observed that the clinical course following diuretic administration, hypersaline infusion, and catheter insertion was both dramatic and revealing (Figure 2). Bladder decompression led to a sustained increase in serum sodium levels. Within a couple of days, sodium levels nearly normalized (134 mmol/L), and the patients' respiratory status improved. The whole history of it became evident clinically that, despite the ongoing pulmonary infection, the earlier refractory hyponatremia and recurrent episodes of ADHF were primarily attributable to neurogenically induced SIADH, which resolved only after the mechanical trigger of urinary retention was eliminated.

This case describes a rare but important association between severe urinary retention and ADHF in a patient with HFpEF. Prolonged and/or marked bladder distention due to urinary tract obstruction activates stretch receptors that stimulate afferent pathways projecting to the hypothalamus, constituting a neurogenic reflex. This, in turn, triggers non-osmotic release of Antidiuretic Hormone (ADH, also called vasopressin), resulting in SIADH. The ensuing inappropriate ADH secretion leads to renal water retention, dilution of serum sodium, and subsequent hyponatremia. In addition, pain caused by bladder distention may further enhance ADH release, thereby worsening the disorder. Impairment of free water excretion due to ADH induces intravascular volume expansion, culminating in volume overload. These mechanisms highlight how urinary tract obstruction can act as an extracardiac neurohormonal trigger that precipitates ADHF (Figure 2).[2-3]

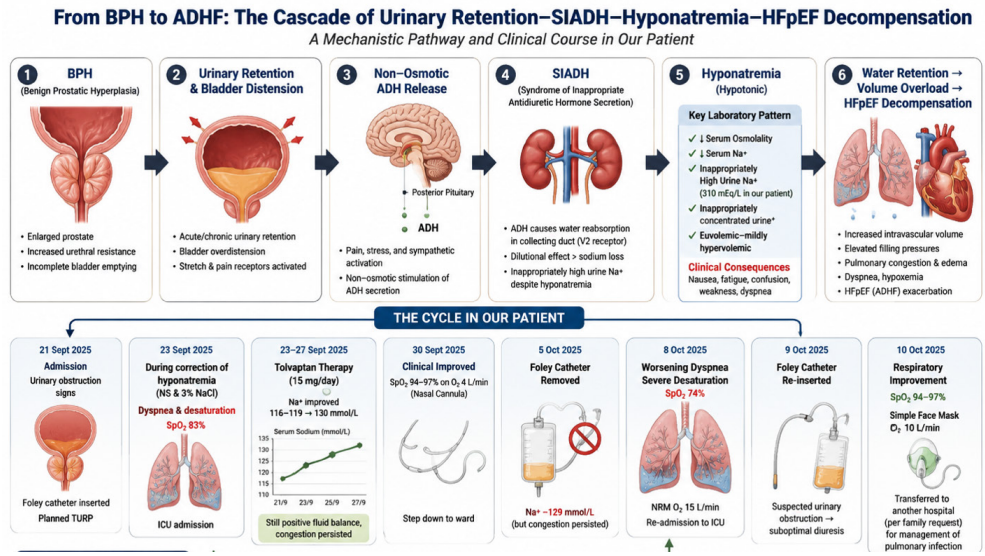

Figure 2. Central illustration.

While there is limited literature specifically addressing ADHF caused by SIADH due to urinary obstruction, some physiologically plausible links exist. Scattered case reports describe urinary obstruction-induced SIADH-like hyponatremia and water retention, which can lead to volume overload. Manappallil et al. (2019) documented a case involving a 60-year-old male patient with a history of BPH who presented with acute urinary retention, confusion, and symptomatic severe hyponatremia. Laboratory assessments revealed findings consistent with SIADH, including decreased serum osmolarity and inappropriately concentrated urine. Imaging and further diagnostic investigations excluded other common etiologies of hyponatremia. Following bladder catheterization and resolution of urinary obstruction, the patient exhibited rapid diuresis and gradual normalization of serum sodium levels, supporting the hypothesis that bladder distention from BPH-associated urinary retention may have

triggered non-osmotic ADH release, resulting in a transient SIADH-like condition.[10] Mahnič et al. (2024) reported the case of an elderly man presenting with severe hypoosmotic hyponatremia associated with acute urinary retention and bladder distension. The laboratory findings were compatible with SIADH, while other common causes of hyponatremia were excluded. The authors proposed that urinary tract obstruction and bladder overdistension triggered non-osmotic ADH release, likely mediated by pain and sympathetic nervous system activation, resulting in water retention and dilutional hyponatremia. Following insertion of a urinary catheter and relief of the obstruction, the patient developed marked post-obstructive diuresis, accompanied by a rapid, spontaneous correction of serum sodium levels without the need for aggressive additional therapy. The report emphasizes that urinary retention is an underrecognized reversible cause of SIADH-like hyponatremia, and that catheter decompression can lead to significant clinical and biochemical improvement, as in our case.[11]

Given the overall clinical picture, we considered the possibility of an alternative mechanism of hyponatremia, particularly in the context of heart failure, and evaluated the impact of saline administration on clinical outcomes. The patient developed worsening congestion and respiratory deterioration during saline correction, indicating hypervolemic hyponatremia associated with ADHF. Nonetheless, the overall evidence indicated that SIADH secondary to urinary tract obstruction remained the primary etiology. At presentation, the patient had urinary obstruction requiring Foley catheter placement – a well – recognized trigger for non-osmotic ADH release via bladder distention and sympathetic nervous system activation. Moreover, serum sodium levels improved substantially following bladder decompression and tolvaptan therapy, as in the previously reported case. Furthermore, episodes of clinical deterioration recurred after Foley catheter removal but were alleviated upon reinsertion, likely due to persistent obstructive pathology limiting effective diuresis. Finally, persistently elevated urinary sodium excretion despite hyponatremia was atypical for classic hypervolemic hyponatremia solely attributable to heart failure, in which renal sodium retention is usually expected.

In a patient with underlying HFpEF and limited diastolic reserve, marked by concentric hypertrophy, the slight increase in volume caused by refractory SIADH was sufficient to push the patient past the Frank-Starling threshold. This resulted in two separate episodes of ADHF, each requiring urgent medical care. The fact that hyponatremia did not improve with fluid restriction and tolvaptan therapy only suggested that the primary trigger, bladder distension, persisted. The rapid and sustained improvement of SIADH, combined with the stabilization of cardiac function after Foley catheter insertion, clearly indicated that BPH-induced urinary retention was the main cause of this complex multisystem presentation. Although definitive confirmation of SIADH was not achieved due to the absence of urine osmolality measurements, the clinical and biochemical improvement following relief of urinary obstruction supports a plausible association between urinary retention, hyponatremia, and recurrent episodes of heart failure decompensation.[1-2,4]

Conclusion

BPH can, on rare occasions, precipitate SIADH, leading to severe and treatment-refractory hyponatremia. In patients with pre-existing cardiac disease, the resulting volume expansion from SIADH may trigger critical, potentially life-threatening episodes of ADHF. This case highlights the importance of recognizing urinary retention as a potential cause of SIADH. It also demonstrates that targeted, non-pharmacological interventions such as bladder decompression can effectively correct the electrolyte disturbance and ameliorate the associated cardiac decompensation.

List of Abbreviations

ADH	Antidiuretic Hormone
ADHF	Acute Decompensated Heart Failure
BPH	Benign Prostatic Hyperplasia
CXR	Chest X-Ray
eRAP	estimated Right Arterial Pressure
HFpEF	Heart Failure with preserved Ejection Fraction
IVC	Inferior Vena Cava
LUTS	Lower Urinary Tract Symptoms
LVEF	Left Ventricular Ejection Fraction
TURP	Transurethral Resection of the Prostate
TTE	Transthoracic Echocardiography
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Author Contributions

All authors contributed to the literature search and review. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declared that they have no competing interests.

Availability of Data and Materials

All data backing this case are included in the manuscript. No extra datasets were created or examined in this study.

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Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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Erratum

Erratum: Dyslipidemia management among patients with high and very high cardiovascular risk in Indonesia: a multi-center registry

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Erratum

Erratum: Comparison of right ventricular global longitudinal strain between pacemaker lead position in patients with permanent pacemaker

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Erratum

Erratum: Mexiletine in the treatment of LQT2, LQT3, and acquired LQTS: a meta-analysis

Dhiya Ihsan Ramadhan[1], Mohammad Iqbal[1], Charlotte Johanna Cool[1], Chaerul Achmad[1], Miftah Pramudyo[1], Hawani Sasmaya Prameswari[1], Mohammad Rizki Akbar[1]

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Erratum

Erratum: Hemodynamic impairment of double culprit ST elevation myocardial infarction, double the trouble: a case report

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Erratum

Erratum: Hemodynamic Conundrum of Thyroid Storm-Induced Acute Heart Failure: Challenging Case in a Remote Area

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