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Original

C–Reactive Protein to Albumin Ratio Predict In–Hospital and Long–term Outcome of ST–Segment–Elevation Myocardial Infarction Patients with SARS–CoV2 Infection Underwent Fibrinolytic Therapy.

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Abstract

Background: The choice of reperfusion therapy in ST-Segment–Elevation Myocardial Infarction (STEMI) patients with COVID-19 is unclear. CRP to Albumin ratio (CAR) was found to be a predictor of thrombus burden. This study was to determine the relationship and predictive value of CAR to in-hospital and long-term outcomes of STEMI patients with COVID-19 treated with fibrinolytic.

Methods: 297 COVID-19 patients with STEMI who underwent fibrinolytic were enrolled. In-hospital outcomes were in-hospital mortality due to cardiovascular death which was divided into mortality <48 hours and >48 hours, fibrinolytic failure, and cardiogenic shock. The presence of reinfarction post-fibrinolytic and mortality after the patient was discharged was assessed as the long-term outcome.

Results: During follow-up, 19.8% experienced in-hospital mortality and 16.1% had reinfarction. In the in-hospital outcome, patients with in-hospital death failed fibrinolytic and cardiogenic shock had higher CAR (6.7±2.4 vs 4.7±1.9; 6.3±1.9 vs 2.1±1.6; 5.5±2.1vs1.8±1.5) with all p-value <0.05. CAR with an optimal cut-off ≥4.46 can be a predictor of fibrinolytic failure with a sensitivity of 86.7% and specificity of 93.6% (PR19.82; 95%CI 10.32-38.06) and predictor of in-hospital death <48 hours with a sensitivity of 84.6% and specificity of 82.7% (PR5.02; 95%CI 3.20-7.90). In the long-term outcome, patients who experienced reinfarction and out-hospital death had higher CAR (5.1±1.2vs2.5±2.4; 5.2±1.3vs2.6±2.4) than those who did not experience the event respectively with all p-value <0.05. CAR with an optimal cut-off ≥3.67 can be a predictor of reinfarction with a sensitivity of 87.5% and specificity of 73.5% (PR12.250; 95%CI 5.38-27.87). The Cox regression model showing CAR ≥3.67 was also associated with higher reinfarction events (p=0.001).

Conclusion: CAR has the potential to be a predictor of in-hospital and long-term outcomes for STEMI patients with COVID-19 which can help determine which patients need more invasive strategies to prevent mortality and morbidity.

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Keywords: STEMI, COVID-19, C-reactive protein to albumin ratio, fibrinolytic, mortality.

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Introduction

Coronavirus disease (COVID-19), has become a global problem affecting the health sector, including patients that required emergency treatment, whereas the healthcare system reduces elective procedures and surgeries to prepare for and manage infected patients.[1] Meanwhile, Ischemic Heart Disease is still one of the non-communicable diseases which is a global problem, where the prevalence worldwide is estimated at 197 million with 9.14 million deaths in 2019 which are most often caused by myocardial infarction. (MI).[2] Due to differences in the characteristics of the acute occlusion that occurs, where the occlusion is total in ST-elevation myocardial infarction (STEMI), STEMI has a higher first 30-day in-hospital mortality compared to Non-ST elevation myocardial infarction (NSTEMI).[3] In addition, STEMI mortality is also influenced by other factors, one of which is the time delay to treatment which is a concern for various current guidelines.[4] What is more, a recent study shows that In-hospital mortality STEMI increased from 5.6% in the second quarter of 2018 to a peak of 8.7% in the first quarter of 2021.[5] Negative impacts of COVID-19 in the management of STEMI patients have been shown by various studies, which are associated with a reduction of catheter activation, increased systematic delay, and also complicated by a high thrombosis burden in patients with concomitant COVID-19 infection, which increases the mortality.[6-8]

Current guidelines highlight the importance of primary percutaneous coronary intervention (PPCI) because the procedure has shown superiority in reducing mortality in STEMI patients through higher rates of achieving TIMI-3 flow and preventing reinfarction.[9,10] However, in this era of the COVID-19 pandemic, various guidelines recommend the choice of fibrinolytic therapy in STEMI patients if the results of the COVID-19 PCR screening test are expected to be out for a long time, which means that STEMI patients with concomitant COVID-19 are preferable to fibrinolytic therapy over PPCI if a COVID-19 cath lab is not available.[1,11]

However, it should be remembered that the effectiveness of fibrinolytic is equal to that of PPCI only in the first 3 hours, and its effectiveness decreases with time due to the density of the thrombus formed.[4] Moreover, patients with cardiovascular disease who are infected with COVID-19 have higher mortality when compared to those who do not have COVID-19, which is associated with high thrombus burdens.[6-8] As has been reported, 73.40% of fibrinolytic failures occur in patients with a high thrombus burden.[11] So, a parameter is needed to determine which STEMI patients with COVID-19 may still be beneficial for fibrinolysis and which cannot be postponed for PPCI.

In COVID-19 conditions where acute inflammation occurs, C-reactive protein (CRP) examination is recommended because CRP is an acute phase protein that increases rapidly within hours of the inflammatory process that can be used to assess the severity of the patient's inflammation.[13] While albumin is a negative acute phase reactant, which inhibits inflammatory and homeostatic processes.[14,15] Low albumin levels are associated with increased mortality and morbidity in CV disease and critically ill patients.[16,19] The CRP to albumin ratio (CAR) is a novel marker that has been found that correlated with disease severity and mortality in patients with COVID-19.[18] Since the severity of inflammation is also associated with atherosclerotic plaque rupture and thrombosis burden, this study aims to investigate whether there is a correlation between CAR and the early and long-term outcome of STEMI patients with COVID-19 infection receiving fibrinolytic therapy.

Methods

In this single-centered retrospective cohort study, the medical records of patients at Prof. I.G.N.G Ngoerah General Hospital, Denpasar in the 2020-2021 period were identified using the International Classification of Diseases, 10th Revision code with a diagnosis of STEMI. Patients whose COVID-19 PCR screening results were positive when diagnosed with STEMI and who received fibrinolytic therapy were included. All patients underwent peripheral blood examination on the first day of hospital admission as the initial procedure for inpatients. The GRACE score for 6 months post-discharge was calculated in all patients. Exclusion criteria included patients with liver dysfunction defined as alanine aminotransferase level >100 (U/L) or chronic liver disease, patients with survival <1 year due to coexisting noncardiac disease such as a tumor, and/or incomplete data. Two hundred

ninety-seven patient data were included in this study. The study was approved by the Ethics Committee of our hospital. In-hospital outcomes were assessed based on the presence of fibrinolytic failure, including the absence of < 50% ST-segment resolution and persistent chest pain after 60–90 minute administration of fibrinolytic agent,[15] cardiogenic shock, and in-hospital death due to cardiovascular death which was then divided into deaths <48 hours and ≥48 hours. While the long-term outcome was assessed after the patients were discharged from the hospital for up to 1 year or until the patient died, based on the presence of reinfarction or rehospitalization of the patients that came back with a diagnosis of myocardial infarction and the presence of cardiovascular death.

All categorical data were presented in frequencies and percentages. The sociodemographic, clinical characteristics, and outcomes are compared using Pearson's chi-square test for categorical variables, and numerical data were compared between the presence or absence of each in-hospital and long-term outcome using the Mann-Whitney U test and the Kruskal Walls test. A cut-off value for CAR in predicting in-hospital mortality <48 hours, CAR and GRACE scores in predicting long-term cardiovascular death were evaluated by receiver operating characteristics (ROC). The hazard ratio (HR) for reinfarction and cardiovascular death based on the cut-off value was calculated and compared using a Cox regression model. In multivariate analysis, we included the variables with statistical significance (P <0.05) in univariate analysis. The goodness-of-fit test for the multivariate logistic regression model was performed using the Hosmer-Lemeshow test. Assessing multicollinearity between the variables was evaluated by calculating variance inflation factors. All statistical analyses were 2-sided and a P value of <0.05 was considered significant. All analyses were performed using IBM SPSS Statistics for Windows, version 26.0.

Result

This study included 297 patients. With a mean age of 58.68 ± 9.5 years and 81.5% male. Demographic, clinical, and laboratory characteristics of all patients are described in **Tables 1** and **Tables 2**. During follow-up, 29.62% had fibrinolytic failure, 21.2% experienced cardiogenic shock, 19.8% experienced in-hospital mortality, 16.1% had reinfarction, and 12.92% experienced cardiovascular death after discharge. Patients who experienced both in-hospital events were more frequently found to have a history of hypertension and previous coronary artery disease (CAD). The prevalence of Killip class rate >2 was significantly higher in patients with in-hospital events than in those without in-hospital outcomes. GRACE scores were significantly higher in the group with long-term outcomes (reinfarction = 202.20 ± 23.96 vs. 187.63 ± 18.11, p=0.000; CV Death = 207.07 ± 25.05 vs. 183.84 ± 12.88, p=0.000).

In laboratory parameters, patients who experienced in-hospital and long-term outcomes had significantly lower albumin, higher CRP, and higher CAR with all p-value <0.05 (**Tables 1** and **Tables 2**). Multivariate analysis in **Table 3** shows that only CRP (OR 1.193), albumin (OR 0.812), CAR (OR 2.888), and GRACE score (OR 2.611) were independently consistently associated with long-term adverse events (including failed fibrinolytic, cardiogenic shock, and in-hospital mortality) and short-term adverse events (including reinfarction and cardiovascular death).

Because CAR and GRACE scores are independent variables that have the strongest relationship with adverse events, then these two parameters are further analyzed through the ROC curve. Analysis of ROC curves for the in-hospital outcome can be seen in **Figure 1**, where CAR with an optimal cut-off ≥4.46 can be a predictor of fibrinolytic failure (AUC: 0.962 [0.939-0.984]) with a sensitivity of 86.7% and specificity of 93.6% and predictor of in-hospital death <48 hours (AUC:0.884 [0.807-0.961]) with a sensitivity of 84.6% and specificity of 82.7%. In long-term outcomes, CAR with an optimal cut-off ≥3.67 can be a predictor of reinfarction (AUC:0.840 [0.796-0.883]) with a sensitivity of 87.5% and specificity of 73.5%; a predictor of CV death post-discharge (AUC:0.841 [0.795-0.886]) with a sensitivity of 91.2% and specificity of 70.7%. Moreover, adding CAR to the GRACE score in predicting reinfarction and CV death gave a better predictive value than the GRACE score alone (Reinfark = AUC:0.781 [0.731-0.831]) vs. AUC:0.577 [0.498-0.656]); CV Death = AUC:0.822 [0.777-0.868]) vs. AUC:0.691 [0.627-0.6756]) **(Figure 2)**.

Patients were divided into 2 subgroups based on the CAR threshold: low (<4.47) and high (≥4.47) for in-hospital outcomes and low (<3.67) and high (≥3.67)

Table 1. Demographic, Clinical, Characteristics and Laboratory Findings of Patients in In-hospital Outcome.

Variable	Fibrinolytic failure (+) (n=88)	Fibrinolytic failure (-) (n=209)	P-value	Cardiogenic Shock (+) (n=63)	Cardiogenic Shock (-) (n=234)	P-value	In-hospital death < 48 hours (n=26)	In-hospital death > 48 hours (n=32)	In-hospital death (-) (n=239)	P-value
Demographic, Clinical, Characteristics										
Age (years)	59.12 ± 8.6	58.49 ± 9.84	0.618	59.52 ± 10.3	58.05 ± 8.8	0.257	57.03 ± 8.34	62.00 ± 9.52	58.41 ± 9.55	0.108
Male gender, n (%)	72 (81.8)	170 (81.3)	0.532	53 (84.1)	189 (80.8)	0.342	19 (73.1)	25 (78.1)	198 (82.8)	0.417
BMI	26.19 ± 3.88	26.12 ± 5.02	0.442	26.02 ± 4.09	26.17 ± 4.86	0.846	26.15 ± 4.78	25.71 ± 3.55	26.20 ± 4.84	0.965
DM, n (%)	27 (30.7)	60 (28.7)	0.417	16 (25.4)	71 (30.3)	0.274	6 (23.1)	11 (34.4)	70 (29.3)	0.643
Hypertension, n (%)	45 (51.1)	50 (23.9)	<0.001	26 (27.4)	37 (18.3)	0.053	19 (73.1)	19 (59.4)	57 (23.8)	<0.001
Previous CAD, n (%)	23 (26.1)	41 (19.6)	0.138	21 (32.8)	42 (18.0)	0.010	1 (3.8)	3 (9.4)	60 (25.1)	0.003
Dyslipidemia, n (%)	13 (14.8)	32 (15.3)	0.530	8 (12.7)	37 (15.8)	0.348	8 (30.8)	3 (9.4)	34 (14.2)	0.052
Smoking, n (%)	16 (18.2)	35 (16.7)	0.442	12 (23.5)	51 (20.7)	0.390	5 (19.2)	5 (15.6)	41 (17.2)	0.936
CKD, n (%)	48 (54.5)	98 (46.9)	0.141	35 (55.6)	111 (47.4)	0.158	15 (57.7)	17 (53.1)	114 (47.7)	0.559
Hyperuricemia, n (%)	13 (14.8)	22 (10.5)	0.199	8 (12.7)	27 (11.5)	0.474	5 (19.2)	3 (9.4)	27 (11.3)	0.445
RHD, n (%)	1 (1.1)	2 (1)	0.653	0 (0)	3 (1.3)	0.488	0 (0)	0 (0)	3 (1.3)	0.692
CHF, n (%)	35 (39.8)	78 (37.3)	0.393	21 (33.3)	92 (39.3)	0.236	13 (50.0)	14 (43.8)	86 (36.0)	0.294
EF %	53.40 ± 13.12	54.59 ± 11.59	0.757	55.10 ± 10.15	54.22 ± 5.67	0.366	52.29 ± 14.20	53.57 ± 13.67	54.54 ± 11.61	0.849
EF <40%, n (%)	14 (15.9)	20 (9.6)	0.088	8 (23.5)	55 (20.5)	0.726	7 (26.9)	4 (12.5)	23 (9.5)	0.031
Systolic Blood	129.15 ± 22.88	119.66 ± 17.10	<0.001	125.36 ± 20.61	121.70 ± 19.10	0.133	126.03 ± 25.11	128.04 ± 25.01	119.95 ± 16.76	0.053
Pressure (mm Hg)	196.35 ± 8.31									
GRACE Score	65 (73.9)	190.00 ± 21.32	0.083	191.43 ± 11.85	190.59 ± 21.62	0.090	214.73 ± 26.93	216.87 ± 24.37	184.61 ± 13.01	<0.001
Killip class >2, n (%)		85 (40.7)	<0.001	43 (28.7)	20 (13.6)	0.001	18 (69.2)	26 (81.3)	106 (44.4)	<0.001
Laboratory Findings										
CRP (mg/L)	184.39 ± 74.52	68.63 ± 57.55	<0.001	211.43 ± 63.10	73.72 ± 59.09	<0.001	222.52 ± 86.00	145.09 ± 55.82	84.28 ± 71.26	<0.001
Albumin (g/dL)	33.58 ± 5.59	38.02 ± 22.66	<0.001	33.97 ± 5.82	37.44 ± 21.54	0.003	33.43 ± 3.56	31.39 ± 5.63	37.77 ± 21.30	<0.001
CAR	5.53 ± 2.18	1.89 ± 1.59	<0.001	6.32 ± 1.93	2.07 ± 1.65	<0.001	6.72 ± 2.65	4.75 ± 1.99	2.32 ± 1.94	<0.001
WBC (103/µL)	7.98 ± 2.31	8.44 ± 5.27	0.478	7.69 ± 2.12	8.46 ± 5.05	0.770	8.25 ± 2.65	7.74 ± 2.03	8.38 ± 5.00	0.813
HB (g/dL)	13.01 ± 1.83	12.89 ± 2.10	0.427	13.08 ± 1.87	12.88 ± 2.06	0.429	12.95 ± 1.62	12.18 ± 2.24	13.02 ± 2.02	0.175
Mo (103/µL)	0.90 ± 1.52	0.78 ± 1.21	0.742	0.90 ± 1.50	0.79 ± 1.26	0.855	0.81 ± 1.11	0.58 ± 0.199	0.85 ± 1.41	0.815
Ne (103/µL)	4.87 ± 2.29	5.82 ± 7.07	0.791	4.64 ± 2.29	5.78 ± 6.72	0.397	5.66 ± 3.42	4.46 ± 1.48	5.67 ± 6.64	0.750
Ly (103/µL)	2.09 ± 0.81	1.91 ± 0.78	0.100	2.12 ± 0.82	1.92 ± 0.78	0.069	2.26 ± 1.04	1.89 ± 0.73	1.94 ± 0.77	0.335
PLT (103/µL)	251.01 ± 73.38	243.70 ± 75.68	0.578	255.26 ± 75.62	243.33 ± 74.73	0.362	275.57 ± 88.61	250.35 ± 72.80	242.03 ± 73.20	0.131
BS (mg/dL)	123.09 ± 57.36	120.90 ± 57.90	0.899	116.69 ± 54.46	125.54 ± 58.51	0.157	127.34 ± 79.15	127.12 ± 54.56	122.80 ± 55.59	0.312
BUN (mg/dL)	16.89 ± 11.81	15.84 ± 11.09	0.476	16.10 ± 12.04	16.17 ± 11.12	0.710	17.38 ± 10.47	16.61 ± 9.93	16.96 ± 11.58	0.474
SC (mg/dL)	1.29 ± 0.82	1.22 ± 0.49	0.681	1.22 ± 0.59	1.24 ± 0.61	0.593	1.22 ± 0.48	1.31 ± 1.07	1.23 ± 0.53	0.784
e-LFG	70.31 ± 23.87	69.50 ± 22.31	0.524	71.73 ± 21.53	69.21 ± 23.08	0.321	68.91 ± 22.66	70.19 ± 24.33	69.85 ± 22.63	0.946
SGOT (U/L)	25.59 ± 25.16	41.73 ± 128.61	0.177	22.75 ± 8.15	40.77 ± 122.41	0.769	21.46 ± 6.90	27.61 ± 35.99	39.88 ± 120.56	0.081
SGPT (U/L)	26.34 ± 26.85	31.99 ± 47.01	0.612	24.66 ± 13.67	31.84 ± 46.79	0.706	25.42 ± 16.77	29.50 ± 40.73	30.96 ± 44.21	0.737

Table 2. Demographic, Clinical, Characteristics and Laboratory Findings of Patients in In-hospital Outcome.

Variable	Reinfarction (+) (n=29)	Reinfarction (-) (n=207)	P-value	Cardiovascular death (+) (n=14)	Cardiovascular death (-) (n=225)	P-value
Demographic and Clinical Characteristics						
Age (years)	58.22 ± 7.98	58.77 ± 9.78	0.651	59.58 ± 8.27	58.56 ± 9.65	0.574
Male gender, n (%)	24 (82.7)	174 (84.1)	0.858	12 (85.7)	186 (82.6)	0.769
BMI	25.50 ± 4.13	26.26 ± 4.80	0.355	25.67 ± 3.37	26.20 ± 4.85	0.654
DM, n (%)	13 (44.8)	57 (27.5)	0.038	7 (50.0)	63 (28.0)	0.089
Hypertension, n (%)	10 (34.4)	47 (22.7)	0.144	4 (8.4)	53 (12.9)	0.669
Dyslipidemia, n (%)	7 (24.1)	27 (13.1)	0.101	4 (28.5)	30 (13.3)	0.125
Smoking, n (%)	8 (27.5)	33 (15.9)	0.126	4 (28.5)	37 (16.4)	0.251
CKD, n (%)	14 (48.2)	100 (48.3)	0.997	9 (64.2)	105 (46.4)	0.208
Hyperuricemia, n (%)	6 (20.7)	21 (10.1)	0.102	4 (28.5)	23 (10.2)	0.046
RHD, n (%)	1 (0.3)	2 (0.01)	0.295	0 (0)	3 (1.3)	0.609
CHF, n (%)	10 (34.4)	76 (36.7)	0.815	9 (64.2)	77 (34.2)	0.031
EF %	53.80 ± 12.07	54.32 ± 12.08	0.855	53.10 ± 11.69	54.38 ± 12.12	0.503
EF < 40%, n (%)	6 (17.6)	42 (16.9)	0.481	4 (11.8)	30 (11.4)	0.566
Systolic Blood Pressure (mm Hg)	122.45 ± 14.89	122.48 ± 20.23	0.554	117.91 ± 13.25	123.06 ± 20.05	0.256
GRACE Score	202.20 ± 23.96	187.63 ± 18.11	<0.001	207.07 ± 25.05	183.84 ± 12.88	<0.001
Laboratory Findings						
CRP (mg/L)	173.30 ± 52.49	89.37 ± 80.04	<0.001	179.44 ± 53.17	93.04 ± 80.17	<0.001
Albumin (g/dL)	34.32 ± 5.56	37.17 ± 20.96	0.050	34.20 ± 5.24	39.03 ± 20.45	0.050
CAR	5.03 ± 1.26	2.57 ± 2.41	<0.001	5.24 ± 1.32	2.68 ± 2.40	<0.001
WBC (103/µL)	8.03 ± 3.24	8.35 ± 4.82	0.703	7.41 ± 2.16	8.41 ± 4.82	0.201
HB (g/dL)	13.31 ± 1.50	12.85 ± 2.10	0.151	13.45 ± 1.48	12.85 ± 2.08	0.083
Mo (103/µL)	0.88 ± 1.52	0.80 ± 1.52	0.861	1.00 ± 1.80	0.79 ± 1.23	0.895
Ne (103/µL)	4.38 ± 1.59	5.76 ± 6.57	0.488	4.15 ± 1.11	5.71 ± 6.42	0.223
Ly (103/µL)	1.86 ± 0.63	1.98 ± 0.82	0.440	1.95 ± 0.57	1.96 ± 0.82	0.858
PLT (103/µL)	227.79 ± 61.10	249.35 ± 76.96	0.053	231.83 ± 64.40	247.68 ± 76.13	0.199
BS (mg/dL)	120.56 ± 48.28	124.26 ± 59.41	0.946	115.14 ± 28.28	124.76 ± 60.41	0.810
BUN (mg/dL)	16.15 ± 14.96	16.16 ± 10.49	0.103	14.11 ± 9.29	16.42 ± 11.52	0.133
SC (mg/dL)	1.28 ± 0.72	1.23 ± 0.58	0.840	1.21 ± 0.52	1.24 ± 0.61	0.638
e-LFG	72.62 ± 24.94	69.19 ± 22.31	0.291	73.62 ± 23.40	69.24 ± 22.66	0.286
SGOT (U/L)	63.40 ± 197.94	31.85 ± 81.07	0.421	41.41 ± 106.35	36.37 ± 109.43	0.391
SGPT (U/L)	31.99 ± 56.90	30.00 ± 38.73	0.818	23.86 ± 18.97	31.15 ± 44.16	0.634

for long-term outcomes. The subgroup findings are presented in **Table 4**, wherein in the subgroup analysis, in-hospital and long-term outcome rates were higher in patients with high CAR than low CAR, with all P-values < 0.01. Cox regression model also showed that CAR ≥3.67 was also associated with higher mortality (P=0.001) and reinfarction (p=0.001) and a significant Hazard Ratio (reinfarction = HR 21.148 95%CI 6.462-69.210; CV Death = HR 15.389 95% CI 6.535-36.237) **(figure 3)**.

Discussion

This study found that CAR was higher in STEMI patients with concomitant COVID-19 infection treated with fibrinolytic who experienced both in-hospital and long-term outcomes. Where CAR can be an independent predictor of in-hospital death due to cardiovascular death <48 hours and reinfarction after discharge. Moreover, CAR improves major adverse cardiac event (MACE) risk stratification which can be more accurate in predicting prognosis if compared to the GRACE score alone, where this finding is in line with other studies that found CAR

Table 3. Cox regression analysis of factors associated to In-hospital and Long-term adverse events.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
In-hospital adverse events (Failed fibrinolytic, cardiogenic shock, and in-hospital mortality)				
Age	1.099 (1.061-1.137)	<0.001	1.205 (1.087-1.337)	0.001
Hypertension	1.068 (1.024-1.114)	0.002	1.627 (0.923- 2.869)	0.092
Previous CAD	2.285 (0.923-4.254)	0.009	1.454 (0.923-2.289)	0.106
CHF	2.285 (1.228-4.254)	0.091	1.215 (0.873-1.689)	0.248
EF <40%	3.057 (1.443-6.473)	0.003	1.315 (0.973-1.776)	0.074
GRACE score	1.215 (1.032-1.431)	0.019	1.159 (1.038-1.294)	0.008
Killip >2	1.124 (1.005-1.257)	0.041	1.059 (1.008-1.126)	0.022
CRP	1.425 (1.118-1.709)	<0.001	1.254 (1.016-1.547)	0.035
Albumin	0.886 (0.810-0.969)	0.008	0.931 (0.873-0.992)	0.029
CAR	1.546 (1.276-1.873)	<0.001	1.787 (1.476-2.163)	<0.001
Dyslipidemia	1.376 (0.650- 2.915)	0.403	Not included	Not included
CKD	1.359 (0.824 -2.241)	0.228	Not included	Not included
Hyperuricemia	1.473 (0.302 - 3.076)	0.302	Not included	Not included
SBP	1.007 (0.981-1.033)	0.601	Not included	Not included
HB	1.007 (0.981-1.033)	0.601	Not included	Not included
Ly	1.008 (0.984-1.032)	0.516	Not included	Not included
PLT	1.024 (0.978-1.072)	0.311	Not included	Not included
BS	1.212 (0.782-1.878)	0.389	Not included	Not included
SGOT	1.224 (0.114-13.152)	0.867	Not included	Not included
Long-term adverse events (Reinfarction and cardiovascular death)				
DM	3.372 (1.141-5.546)	0.022	2.876 (1.173-7.051)	0.021
Hyperuricemia	6.642 (2.102-20.993)	0.001	1.441 (0.531-3.915)	0.473
GRACE score	3.277 (1.265-8.489)	0.014	2.611 (1.551-4.395)	<0.001
CRP	1.483 (1.098-2.003)	0.011	1.193 (1.071-1.328)	0.013
Albumin	0.927 (0.871- 0.987)	0.017	0.812 (0.641-1.028)	0084
CAR	3.432 (1.345-8.757)	0.009	2.888 (1.767-4.721)	<0.001
Hypertension	1.791 (0.779-4.116)	0.169	Not included	Not included
Dyslipidemia	2.121 (0.827-5.441)	0.117	Not included	Not included
Smoking	1.357 (0.691-2.663)	0.374	Not included	Not included
CKD	1.748 (0.566-5.394)	0.331	Not included	Not included
CHF	3.039 (0.053-9.397)	0.053	Not included	Not included
WBC	1.321 (0.792-2.203)	0.286	Not included	Not included
HB (g/dL)	0.812 (0.643- 1.025)	0.081	Not included	Not included
Ne	1.209 (0.983- 1.487)	0.072	Not included	Not included
PLT	1.809 (0.881- 3.714)	0.106	Not included	Not included
BUN	1.095 (0.889- 1.348)	0.393	Not included	Not included

Table 4. Demographic, Clinical Characteristics, and laboratory findings of Patient With High or Low CAR.

Variable	High CAR	Low CAR	P-value
Demographic and Clinical Characteristics (High CAR >4.46, n=69. Low CAR n=228)			
Age (years)	58.89 ± 8.36	58.61 ± 9.83	0.826
Male gender, n (%)	59 (85.5)	183 (80.3)	0.212
BMI	25.97 ± 4.01	26.19 ± 4.90	0.718
DM, n (%)	18 (26.1)	69 (30.3)	0.308
Hypertension, n (%)	28 (40.6)	67 (29.4)	0.056
Previous CAD, n (%)	23 (33.3)	41 (18.0)	0.007
Dyslipidemia, n (%)	9 (13.0)	36 (15.8)	0.365
Smoking, n (%)	16 (23.2)	35 (15.4)	0.094
CKD, n (%)	37 (53.6)	109 (47.8)	0.239
Hyperuricemia, n (%)	9 (13.0)	26 (11.4)	0.426
RHD, n (%)	0 (0)	3 (1.3)	0.451
CHF, n (%)	26 (37.7)	87 (38.2)	0.530
Others, n (%)	10 (14.5)	34 (14.9)	0.933
EF	53.35 ± 12.14	54.51 ± 12.04	0.484
EF <40%, n (%)	10 (14.5)	24 (10.5)	0.240
Systolic Blood Pressure (mm Hg)	124.11 ± 20.71	121.98 ± 19.07	0.294
GRACE Score	202.55 ± 25.41	187.14 ± 17.06	<0.001
Killip class >2, n (%)	49 (71.0)	101 (44.3)	<0.001
Demographic and Clinical Characteristics (High CAR >4.46, n=69. Low CAR n=228)			
CRP (mg/L)	216.97 ± 56.60	68.42 ± 52.06	<0.001
Albumin (g/dL)	34.04 ± 5.78	37.51 ± 21.80	0.004
CAR	6.46 ± 1.73	1.92 ± 1.44	<0.001
WBC (103/µL)	7.77 ± 2.03	8.46 ± 5.12	0.948
HB (g/dL)	12.93 ± 1.95	12.92 ± 5.02	0.862
Mo (103/µL)	0.86 ± 1.43	0.80 ± 1.27	0.845
Ne (103/µL)	4.71 ± 2.17	5.79 ± 6.81	0.854
Ly (103/µL)	2.12 ± 0.82	1.91 ± 0.78	0.058
PLT (103/µL)	251.64 ± 73.87	244.12 ± 75.35	0.665
BS (mg/dL)	120.07 ± 52.74	124.75 ± 59.18	0.960
BUN (mg/dL)	15.78 ± 9.55	16.27 ± 11.79	0.970
SC (mg/dL)	1.19 ± 0.42	1.25 ± 0.65	0.753
e-LFG	71.42 ± 21.62	69.23 ± 23.10	0.387
SGOT (U/L)	22.27 ± 7.72	41.40 ± 123.96	0.558
SGPT (U/L)	23.43 ± 11.79	32.41 ± 47.43	0.927
Demographic and Clinical Characteristics (High CAR >4.46, n=69. Low CAR n=228)			
Failed Fibrinolytic	54 (78.3)	9 (3.9)	<0.001
Cardiogenic Shock	59 (85.5)	29 (12.7)	<0.001
CV Death <48h	20 (28.9)	6 (2.6)	<0.001
Demographic and Clinical Characteristics (High CAR >3.67, n=108. Low CAR n=189)			
Reinfarction	42 (38.9%)	6 (3.2%)	<0.001
CV Death	31 (28.7%)	3 (1.6%)	<0.001

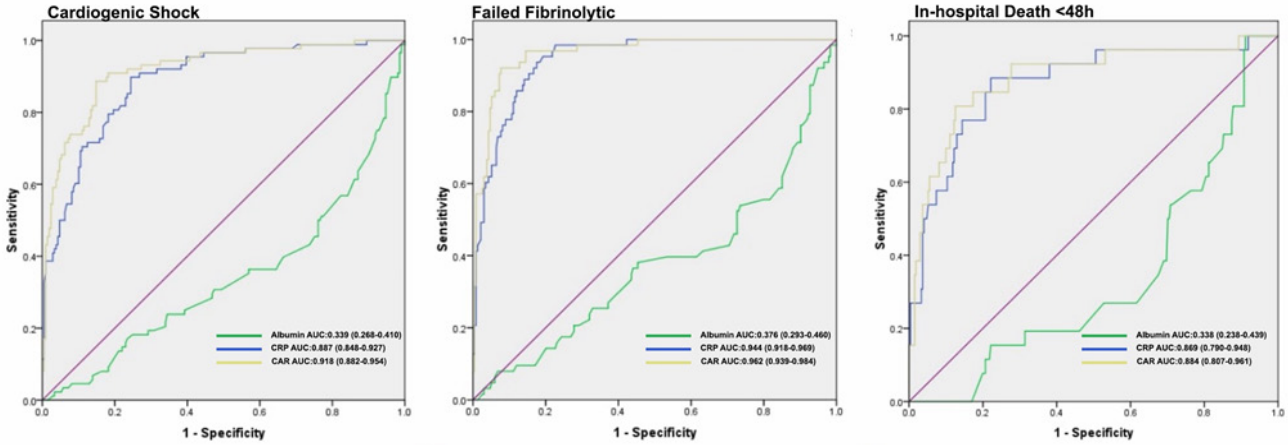

Figure 1. Receiver operating characteristic (ROC) curves for the albumin, C-reactive protein (CRP), and CRP to albumin ratio (CAR) for predicting in-hospital outcomes.

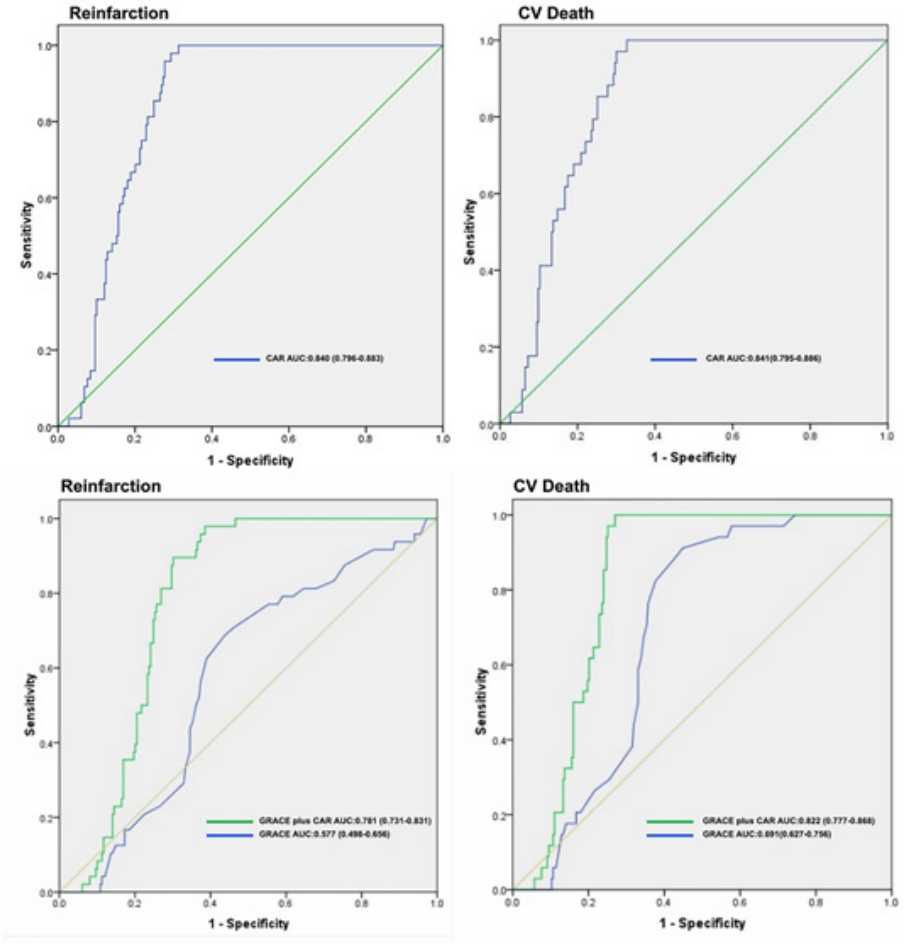

Figure 2. Receiver operating characteristic (ROC) curves for C-reactive protein (CRP) to albumin ratio (CAR), The Global Record for Acute Coronary Events (GRACE) score, GRACE score plus CAR for predicting Long-term outcomes.

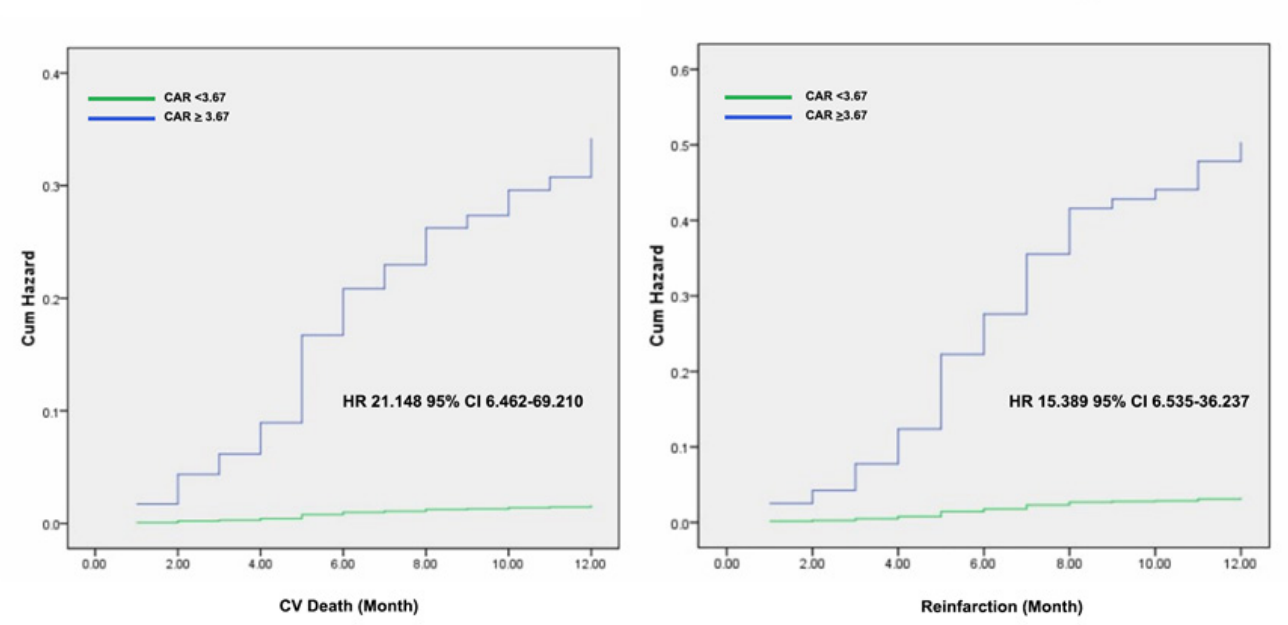

Figure 3. Hazard ratio curve for long-term outcomes according to Optimal cut-off of C-reactive protein (CRP) to albumin ratio (CAR).

can predict outcomes of STEMI patients, but who underwent PCI and outcomes of general patients with COVID-19 infection.[17-20] Consistent with our findings which conclude high CAR is associated with poor in-hospital and long-term outcomes, Rencuzogullari et al, reported a significantly higher pre-procedure PPCI CAR associated with findings of no-reflow phenomena on angiography and an independent variable associated with in-stent restenosis after 21.07±3.89 months (OR 2.289. 95% CI 1.056-4.959).[17] They suspect an acute MI that triggers inflammation and can last weeks to months. On the other hand, a dramatic increase in CAR was also reported in a recent meta-analysis in populations with severe COVID-19 (MD 1.69) and non-survivor COVID-19 (MD 2.59) because it can accurately describe the patient's inflammatory status.[18] This is also supported by a cohort study that reported the predictive value of CAR (AUC 0.922, 95% CI 0.862-0.981) which was comparable to Interleukin-6 (IL-6) (AUC 0.955, 95% CI 0.912-0.997) in COVID-19.19 CAR is relatively more widely available, so it is a valuable biomarker in everyday clinical practice.

SARS-CoV-2 caused COVID-19, uses the angiotensin-converting enzyme-2 receptor as a portal to enter the target cells, including endothelial and cardiac myocytes, so that the cardiac tissues become the target of SARS-CoV-2.[21] Little is known about the pathophysiology of STEMI in SARS-CoV-2 infection. It is suspected to involve various mechanisms, including direct myocardial injury, plaque rupture due to severe acute inflammation, changes in the supply and demand ratio, and coronary thrombosis. Coronary thrombosis occurs because COVID-19 facilitates the occurrence of severe thrombosis in the coronary arteries by inducing a hypercoagulable state.[22] Triggered inflammatory mediators such as IL-6 and CRP also play an important role in causing a 'cytokine storm' in the setting of acute inflammation and are reported to directly triggered disruption of atherosclerotic plaque and also associated with the severity of the infarct.[23,24]

CRP is one of the most established markers of cardiovascular disease.[25] CRP levels have been associated with vascular stiffness, atherosclerosis, and end-organ damage.[26] In various studies, CRP level at admission is associated with increased short- and long-term MACE in patients with the acute coronary syndrome (ACS) and COVID-19 patients, and in these patients that had higher CRP levels than the survivors, which

is in line with the findings in our study.[18,27-29] Albumin is a negative acute phase protein that has protective effects, such as anti-inflammatory and vasodilator. Albumin has antithrombotic effects, including reduced release of thromboxane A2, increased conversion of prostaglandin (PG) H2 to PGD2, and increased release of platelet-activating factor, all of which inhibit platelet aggregation.[30,31] Albumin also has antioxidant activity that supports suppression of free radicals that can increase vascular damage, which leads to atherosclerosis and increases fibrinolysis which will inhibit the binding of fibrinogen to endothelial cells.[30,31] Thus, low albumin may induce a prothrombotic environment, which has been considered as an impact of COVID-19 that also affects atherosclerotic plaques.[32] In line with the findings of low albumin in patients with short-term and long-term outcomes in our study, previous studies have also shown that low serum albumin levels are a negative predictor of prognosis in patients with ACS and COVID-19.[33,34]

The combined use of CRP and albumin might be a better prognostic marker in predicting outcomes in various diseases. The CAR represents the balance between CRP and albumin and also can assess the patient's inflammatory and nutritional status.[35,36] When the values of the two markers change, the ratio can change concordantly, but the CAR offers higher precision than using either marker alone. The combination of albumin and CRP into one index has been proposed and other studies have also shown that CAR is more consistent with prognosis than CRP or albumin levels alone.[37,38]

An important finding in this study is that CAR can predict reinfarction and out-of-hospital mortality within one year. This finding is in line with the study conducted by Acet et al,[17] who found that CAR was significantly associated with MACE, which is mortality, cardiogenic shock, and reinfarction. The study also showed a higher correlation between CAR in the group with a high SYNTAX score when compared to those with a lower SYNTAX score, so it can be assumed that CAR also represents high coronary atherosclerotic burden and lesion complexity so that it is associated with the incidence of mortality and reinfarction in 1 year in STEMI patients, this is also exacerbated by COVID-19 infection that reducing the ability of fibrinolytic therapy to achieve TIMI-3 flow which in the absence of COVID-19 infection alone is only 50-60%, and reported after the recovery from COVID-19, the inflammatory process, prothrombotic and hypercoagulation can persist for a long time.[17,39-42] It makes sense that in this study that patients with high CAR, which also indicates the severity of COVID-19 infection, had higher mortality and reinfarction as well.

In the in-hospital outcome, the condition of COVID-19 infection represented by CAR is also thought to play a role in the outcome of STEMI patients where severe thrombosis and hypercoagulation are associated with the severity of the disease. In the COVID-19 era, also patients often experience systemic delays in time to presentation which can lead to older (and more organized) clots, which will decrease the efficacy of fibrinolytic therapy and increase the risk of fibrinolytic failure resulting in increased myocardial damage and decreased myocardial reserve leading to patients falling into critical conditions such as cardiogenic shock and increasing hospital mortality as in our study.[22,42-44]

The GRACE score is a good tool for risk stratification in patients with ACS and can be used to predict risk but is limited to 6 months after hospital discharge only.4 Our study shows that the GRACE risk score predicts long-term outcomes at follow-up up to 1 year in STEMI patients with lower sensitivity and specificity than CAR, and this risk scoring system excludes markers of oxidative stress and inflammation. The addition of oxidative stress parameters such as nitrite/nitrate and superoxide dismutase to the GRACE score has been shown to predict MACE progression better than the GRACE score alone.[45] In addition, it has been shown that the combination of CRP with the GRACE score provides more accurate prognostic information in patients with ACS.[46] Our study found that adding the CAR to the GRACE risk score system could increase the predictive value of the GRACE score in the estimation of prognosis in STEMI patients undergoing fibrinolytic therapy at 1 year.

Conclusion

The present study showed that CAR has the potential to be a predictor of in-hospital and long-term outcomes for STEMI patients with COVID-19 treated with fibrinolytic therapy, which can help determine which STEMI COVID-19 patients require more invasive strategies than fibrinolytic therapy to prevent mortality and morbidity.

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