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Assessment of C-Reactive Protein/Serum Albumin Ratio in Relation to Acute Presentation and Early Outcome of Patients with Acute Coronary Syndrome

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Abstract

Background: Acute coronary syndrome (ACS) is the leading cardiovascular (CV) cause of mortality. C reactive protein (CRP) has linked with long-term risk of recurrent cardiovascular events or death. Albumin, in contrast to CRP known as a negative acute-phase protein. Thus a newly introduced marker assessed relation of CRP to albumin ratio (CAR), which may provide better results than the use of either marker alone. The aim of the study is to assess the association of C-reactive protein to albumin ratio (CAR) with in-hospital short-term major adverse cardiac events (MACEs) in acute coronary syndrome (ACS) patients. **Patients & Methods:** A multi-centers prospective cohort study was conducted at coronary intensive care units (CICU) in Baghdad during the period from March to October 2021 that included a total of 132 patients who were diagnosed as a case of ACS. They were assessed for major adverse cardiac events (MACEs) like cardiogenic shock, arrhythmias, post-MI angina, and acute heart failure while inside the ward, in addition to need for early interventional therapeutic approach in relation to (CAR) immediately at time of admission to hospital. **Results:** High values of CAR, whether using hs-CRP or CRP, were identified as an independent predictor for in-hospital MACEs (P value < 0.001 and 0.002 respectively. A cut-off value of CAR (using hs-CRP) is 3.18 mg/L in context of discrimination between medically treated ACS patients and death outcome in term of high CAR. A cut-off value of CAR (using CRP) as 9.13 mg/L suggests the usefulness in discrimination of outcome in relation to medically managed patients, at presentation. CAR had a positive significant correlation with hospital stay (r = 0.210, P = 0.036). **Conclusion:** The CAR was independently correlated with in-hospital short-term MACEs and can be used for risk stratification in patients with ACS.

Keywords

Acute Coronary Syndrome, Cardiac Events, C Reactive Protein, Albumin

1. Introduction

Acute coronary syndrome (ACS), the leading cause of mortality worldwide, refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction [1].

It is known that inflammation plays a major role in pathogenesis of onset and progression of atherosclerosis. The culprit lesion that precipitates the acute event is usually a complex ulcerated or fissured atheromatous plaque with adherent platelet-rich thrombus and local coronary artery spasm. In acute MI, occlusive thrombus is almost always present at the site of rupture or erosion of an atheromatous plaque [2].

The prognosis of patients who have survived an acute coronary syndrome is related to the extent of residual myocardial ischemia, the degree of myocardial damage and the presence of ventricular arrhythmias. Half the deaths occur within 24 hours of onset of symptoms and about 40% of all affected patients die within the first month [3].

Patients with unstable angina have a mortality of approximately half that of patients with MI. Patients with non-ST-elevation myocardial infarction (NSTEMI) who has ST segment depression of 1 mm or greater in two or more leads are almost four times as likely to die within 1 year, and the patient with ST segment depression of 2 mm or greater in magnitude is almost six times as likely to die within 1 year. If ST segment depression of 2 mm or greater is present in more than one region of the ECG, the mortality is increased 10-fold. Although in-hospital mortality is higher in patients with ST segment elevation MI than among those with NSTE ACS (7 vs. 5%, respectively), the mortality rates at 6 months are similar for the two conditions (12 vs. 13%, respectively) and during long-term follow-up of patients hospitalized with ACS, rates of death are actually higher in those with NSTE ACS than in those with ST-elevation myocardial infarction (STEMI) [4]. Of those who survive an acute attack, more than 80% live for a further year, about 75% for 5 years, 50% for 10 years and 25% for 20 years [3].

Cardiac biomarkers play critical roles in the diagnosis and prognosis of AMI. like Myocardial necrosis biomarkers Cardiac troponin T (cTnT) and I (cTnI), Myoglobin, Heart-type fatty acid binding protein (hFABP) in addition to ischemia-modified albumin [5].

In acute ischemia, the N terminus of albumin is altered, thereby reducing its binding capacity, and the resultant protein is referred to as ischemia-modified albumin (IMA). In patients with suspected ACS, the diagnostic accuracy at presentation increased when IMA was used in conjunction with cTnT and ECG

findings. IMA in combination with initial cTnT is more sensitive than the latter alone for predicting adverse cardiac events.

Other inflammatory markers had used also for this purpose like CRP is a significant predictor of poor outcome. Studies confirmed that a higher CRP level is associated with increased long-term risk of recurrent cardiovascular events or death [6]. C-reactive protein (CRP) is one of the acute-phase proteins (APPs), which are those whose serum level increases or decreases by at least 25% during inflammatory conditions [6].

Both C-reactive protein (CRP) and albumin, known as positive and negative acute phase reactants (APRs), respectively, are synthesized by hepatocytes, and their serum levels can be measured [7]. The newly introduced parameter, CRP to albumin ratio (CAR), which is indicative of the balance of CRP and albumin, may provide better results in evaluating the inflammatory status than the use of either marker alone. The C-reactive protein (CRP)/albumin (Alb) ratio (CAR) has been identified as a novel inflammation-based prognostic marker in several cancers, including esophageal cancer, lung cancer, hypopharyngeal and laryngeal cancer, and nasopharyngeal cancer [8] [9] [10] [11]. Some studies have also shown that CAR is associated with cardiovascular diseases. Yücel *et al.* stated that an elevated CRP/albumin ratio was independently associated with advanced Heart failure and poor hemodynamic parameters [12].

The aim of study is to assess the association of C-reactive protein to albumin ratio (CAR) with in-hospital short-term major adverse cardiac events (MACEs) in acute coronary syndrome (ACS) patients.

2. Patients and Method

Study design: Multi-centers and prospective cohort study conducted at coronary intensive care units (CICU) in Baghdad during the period from March to October 2021. It is performed in line with the principles of the Declaration of Helsinki and approved by ethical committee of Iraq board for medical specialization (National academic committee).

Study population: It included (132) patients with ACS diagnosis according to AHA/ACCF guidelines (according to symptoms, ECG findings and serum troponin levels), who had admitted to the CICU.

Patients with severe hepatic diseases, estimated glomerular filtration rate < 15 ml/kg/m^2, chronic heart failure (NYHA class > II), malignancy, valvular heart disease, concomitant acute stroke or inflammation, venous thromboembolism were excluded. Patients, who were lost to follow-up were also excluded

Data Collection: Venous blood samples were instantly collected on admission to the hospital. In addition to serum troponin assay, other—biochemical profiles—including CRP and albumin levels were evaluated for some patients while, Hs-CRP and albumin levels were measured for others according to availability and each center workup.

CAR is calculated manually according to the following formula: C-reactive

protein to Albumin Ratio = CRP/ALBUMIN.

Normal standard range for, hs-CRP < 5 mg/L, CRP < 10 mg/dL, S. Albumin 3.2 - 4.8 g/dL according to reference of manufacturer pamphlet

In-hospital cardiac events and treatment outcomes: A short follow-up observation was designed in this study setting looking for in-hospital adverse cardiac events and treatment modalities (medical conservative or interventional approach) as well as early outcome. The major adverse cardiac events (MACEs) were defined as cardiogenic shock, arrhythmias, post-MI angina, acute heart failure and all-cause death [13]. A treatment outcome was recorded as in-hospital patient's death, discharge with improvement or referred for further intervention.

Data Statistical analysis: Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to normality test (Shapiro Wilk test), Data with normally distribution were presented as mean and standard deviation, and analyzed with Student t-test. Data with non-normal distribution were presented as median and range and analyzed with Mann Whitney U test (for two groups comparison) or Kruskal Wallis (for three groups comparison). Categorical variables were expressed as number and percentage and analyzed with Chi-square test. Receiver operating characteristic (ROC) curve was used to evaluate CAR in the context of discrimination between medically-treated and died patients or between medically-treated and PCI-treated patients. Spearman's correlation test was used to explore the possible correlation of hs CRP and CRP with each of age, disease duration and hospital stay. A P-value less than 0.05 was considered to indicate a statistically significant difference.

Ethical consideration: All patients were informed about the study and consent was taken to be included in this study. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

3. Results

3.1. General Description of Patients Group Characteristics

A total of 132 patients were distributed according to which biochemical assessment had used, those 100 patients who performed hs-CRP assay were labeled as group I while the rest 32 patient had performed CRP labeled as group II.

The age group of patients sample ranges from (30 - 85) years old with a mean of (58.85 ± 11.97).

The duration of hospital stay range is (1 - 9) days with a mean (5.14 ± 1.61).

Eighty-one (81) patients (61.36%) got no cardiac events while their admission, distributed as 58 patients within group I and 23 patients in group II. The rest patients had a major cardiac events as complication in form of, acute heart failure represent (26) 19.7%, arrhythmia (16) 12.12%, post-MI angina (10) 7.58% and cardiogenic shock (10) 7.58%.

Regarding treatment outcomes, 85 patients were treated medically and formed

(64.39%) with (62%) in group I in comparison to 71.88 in group II, PCI was indicated for 36 (27.27%) patients with (30%) in group I in comparison to group II; However, death was reported in 11 (8.33%) with (8%) in group I in comparison to (9.38%) in group II (Table 1).

3.2. Comparison of Biochemical Profiles in Both Patients Groups

Group I patients showed a range of hs-CRP (0.5 - 40.0) with a mean 9.23 ± 8.09 mg/L, while group II patients showed a range of CRP (0.5 - 100) with a mean 13.33 ± 24.95 mg/L, with no statistical significance (P value 0.108).

Calculation of CAR ratio reveals that mean for group I (2.32 ± 2.1) and group II (3.36 ± 6.28) with no statistical significance (P value 0.130), (Table 2).

Relationship between CAR using hs-CRP in group I patients reveals that neither any of demographic, nor any of clinical characteristics had shown any statistical significance with CAR unlike its implication with ACS complications as there was very high statistical significance with Cardiac event (P value < 0.001), acute heart failure (P value 0.001), as well as statistical significance with other complications like arrhythmia and cardiogenic shock (P value 0.031 for both) (Table 3).

Similarly this CAR has a clear statistical significant relationship with clinical outcome especially when mode of management continued with conservative treatment despite high CAR compared with those offered PCI during acute presentation (P value 0.002), (Table 3).

Accordingly a cut-off value of CAR (using hs-CRP) is considered statistically to be 3.18 mg/L with sensitivity of 75% and specificity of 82% (95% confidence interval 0.759 - 0.949), in context of discrimination between medically treated ACS patients and death outcome in term of high CAR.

Similarly, in same clinical application making benefit of this CAR in defining what is appropriate management line, statistical analysis reveals a critical predictive cutoff value of 1.4 mg/L to make a decision of continuing conservative medical management or referral to PCI with sensitivity 67% and specificity 53%, (95% CI = 0.50 - 0.75).

In **group II** statistical analysis in assessing CAR (using CRP) in relationship with other characteristics reveals that, none of demographic or clinical features had shown any statistical significance unlike its relationship with cardiac event (P value < 0.002), acute heart failure (P value 0.001), as well as statistical significance with complications like cardiogenic shock (P value 0.002). Patient's outcome had also a clear relationship in term of management mode in view of CAR levels (P value 0.012), (Table 4).

The clinical application of CAR (using CRP) in group II patients suggests the usefulness in discrimination of outcome in relation to medically managed patients when considering cut off value of CAR = 9.13 mg/L at presentation with 100% sensitivity and specificity (95% CI = 1.0 - 1.0).

Similarly, a predictive cut-off value of CAR (using CRP) had concluded to help in making management mode decision between conservative medical

Table 1. Demographic and clinical characteristics of the patients.

Variables	Total (n = 132)	Group I hs CRP (n = 100)	Group II CRP (n = 32)
Age, years			
Mean ± SD	58.85 ± 11.97	57.85 ± 11.65	61.97 ± 12.58
Range	30 - 85	30 - 85	40 - 82
Gender			
Male	87 (65.91%)	67 (67%)	20 (62.5%)
Female	45 (34.09%)	33 (33%)	12 (37.5%)
Male: female ratio	1.93:1	2.03:1	1.67:1
Smoking			
Never	35 (26.52%)	28 (28%)	7 (21.88%)
Current	71 (53.79%)	53 (53%)	18 (56.25%)
Ex-smoker	26 (19.7%)	19 (19%)	7 (21.88%)
Comorbidities			
None	14 (10.61%)	10 (10%)	4 (12.5%)
DM	93 (70.45%)	68 (68%)	25 (78.13%)
HTN	68 (51.52%)	53 (53%)	15 (46.88%)
CAD	26 (19.7%)	22 (22%)	4 (12.5%)
Disease duration, m			
Mean ± SD	16.6 ± 23.33	17.14 ± 23.92	14.87 ± 21.66
Range	1.0 - 96	1.0 - 96	1.0 - 72
Hospital stay, days			
Mean ± SD	5.14 ± 1.61	5.27 ± 1.62	4.75 ± 1.55
Range	1.0 - 9.0	1.0 - 9.0	2.0 - 9.0
Cardiac events			
None	81 (61.36%)	58 (58%)	23 (71.88%)
Acute heart failure	26 (19.7%)	21 (21%)	5 (15.63%)
Arrhythmia	16 (12.12%)	12 (12%)	4 (12.5%)
Post-MI angina	10 (7.58%)	9 (9%)	1 (3.13%)
Cardiogenic shock	10 (7.58%)	7 (7%)	3 (9.38%)
Outcomes			
Medical treatment	85 (64.39%)	62 (62%)	23 (71.88%)
PCI	36 (27.27%)	30 (30%)	6 (18.75%)
Death	11 (8.33)	8 (8%)	3 (9.38%)

Table 2. Comparison of biochemical profiles (CRP, albumin and CAR) in both patients groups.

Variables	Group I hs CRP (n = 100)	Group II CRP (n = 32)	P-value
CRP/hs CRP, mg/L			
Mean ± SD	9.23 ± 8.09	13.33 ± 24.95	0.108‡
Median	6.85	4.0	
Range	0.5 - 40.0	0.5 - 100	
Albumin, g/dl			
Mean ± SD	4.03 ± 0.34	3.98 ± 0.38	0.454†
Range	3.2 - 5.0	3.3 - 5.0	
CAR			
Mean ± SD	2.32 ± 2.1	3.36 ± 6.28	0.130‡
Median	1.54	1.05	
Range	0.12 - 10.81	0.13 - 28.57	

†Student t-test, ‡Non-parametric Mann Whitney U test. CRP: C-reactive protein, CAR: C-reactive protein/albumin ratio.

Table 3. Association of CAR with demographic and clinical characteristics of the patients in hs CRP group (Group I).

Variables	CAR	P-value‡
Gender		
Male	1.46 (0.12 - 10.81)	0.422
Female	2.25 (0.12 - 6.75)	
Smoking		
Never	2.28 (0.12 - 8.75)	0.768
Current	1.43 (0.26 - 10.81)	
Ex-smoker	1.6 (0.14 - 5.26)	
Comorbidities		
Present	1.57 (0.12 - 10.81)	0.991
Absent	1.37 (0.13 - 8.75)	
DM		
Present	1.68 (0.12 - 8.75)	0.471
Absent	1.12 (0.13 - 10.81)	
HTN		
Present	1.67 (0.14 - 10.81)	0.581
Absent	1.46 (0.12 - 8.75)	

Continued

CAD		
Present	1.84 (0.32 - 10.81)	0.139
Absent	1.43 (0.12 - 8.75)	
Cardiac events		
Present	0.97 (0.12 - 8.75)	<0.001
Absent	0.97 (0.12 - 8.75)	
Acute heart failure		
Present	2.93 (1.09 - 10.81)	0.001
Absent	1.43 (0.12 - 8.75)	
Arrhythmia		
Present	3.59 (0.24 - 8.75)	0.031
Absent	1.43 (0.12 - 10.81)	
Post-MI angina		
Present	1.67 (1.04 - 6.75)	0.474
Absent	1.53 (0.12 - 10.81)	
Cardiogenic shock		
Present	3.53 (2.22 - 8.75)	0.031
Absent	1.43 (0.12 - 10.81)	
Outcomes		
Medical treatment	1.27 (0.12 - 8.75)[a]	0.002
PCI	2.14 (0.26 - 10.81)[b]	
Death	3.64 (2.22 - 8.75)[b]	

[‡]Data were expressed as median and range and compared using Mann Whitney U test. Different small letters indicate significant differences. DM: diabetes mellitus, HTN: hypertension, CAD: coronary artery disease.

Table 4. Association of CAR with demographic and clinical characteristics of the patients in CRP group (Group II).

Variables	CAR	P-value[‡]
Gender		
Male	0.88 (0.24 - 18.0)	0.346
Female	1.27 (0.13 - 28.57)	
Smoking		
Never	0.95 (0.26 - 28.57)	0.512
Current	0.74 (0.24 - 15.48)	
Ex-smoker	1.65 (0.13 - 18.0)	

Continued

Comorbidities		
Present	1.0 (0.13 - 28.57)	0.230
Absent	2.25 (0.73 - 4.84)	
DM		
Present	0.95 (0.13 - 28.57)	0.721
Absent	1.08 (0.25 - 4.84)	
HTN		
Present	0.79 (0.24 - 28.57)	0.313
Absent	1.19 (0.13 - 18.0)	
CAD		
Present	1.54 (0.25 - 2.0)	0.805
Absent	1.0 (0.13 - 28.57)	
Cardiac events		
Present	4.14 (0.24 - 28.57)	0.002
Absent	0.74 (0.13 - 4.84)	
Acute heart failure		
Present	15.47 (1.17 - 28.57)	0.001
Absent	0.79 (0.13 - 4.84)	
Arrhythmia		
Present	3.57 (0.24 - 18.0)	0.279
Absent	1.0 (0.13 - 28.57)	
Post-MI angina		
Present	1.81 (1.82 - 1.82)	0.563
Absent	1.03 (0.13 - 28.57)	
Cardiogenic shock		
Present	15.47 (11.43 - 28.57)	0.002
Absent	0.95 (0.13 - 18.0)	
Outcomes		
Medical treatment	0.79 (0.13 - 4.84)[a]	0.012
PCI	2.25 (0.26 - 18.0)[b]	
Death	15.48 (11.43 - 28.57)[b]	

[‡]Data were expressed as median and range and compared using Mann Whitney U test. Different small letters indicate significant differences.

treatment from those indicated for immediate intervention PCI considering value of 0.78 mg/L with sensitivity and specificity of the test were 67% and 78%, respectively (95% CI = 0.37 - 0.97).

3.3. Correlation between CAR and Other Clinical Variables

Spearman's correlation was used to explore the possible correlation of CAR in both groups with other clinical variables. In group II, CAR demonstrated a positive significant correlation with age (r = 0.459, P = 0.008). On the other hand, CAR had a positive significant correlation with hospital stay (r = 0.210, P = 0.036) in group I (Figure 1, Figure 2). While no correlation found between disease duration with neither hs-CRP nor CRP (r = −0.074, P = 0.644) (r = −0.119, P = 0.515) respectively.

4. Discussion

High values of CAR, whether using hs-CRP or CRP, were identified as an

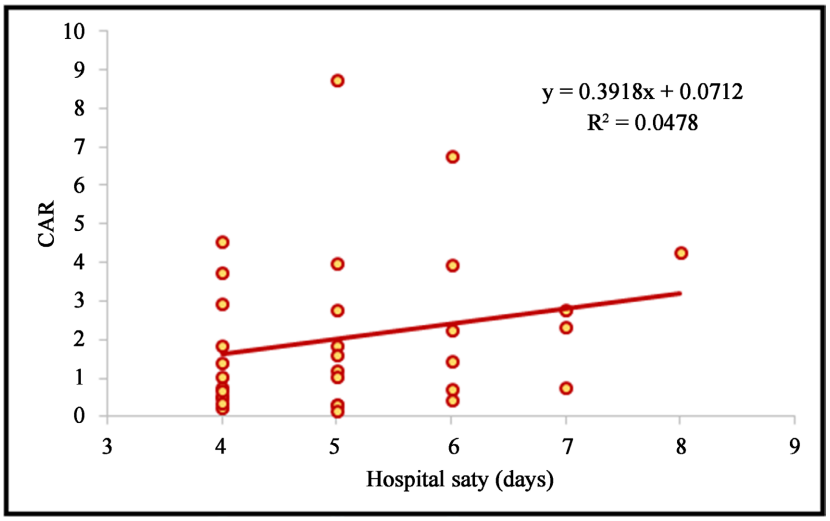

Figure 1. Correlation between CAR levels and hospital stay duration in group I according to scatter plot and regression line (P = 0.036, r = 0.210).

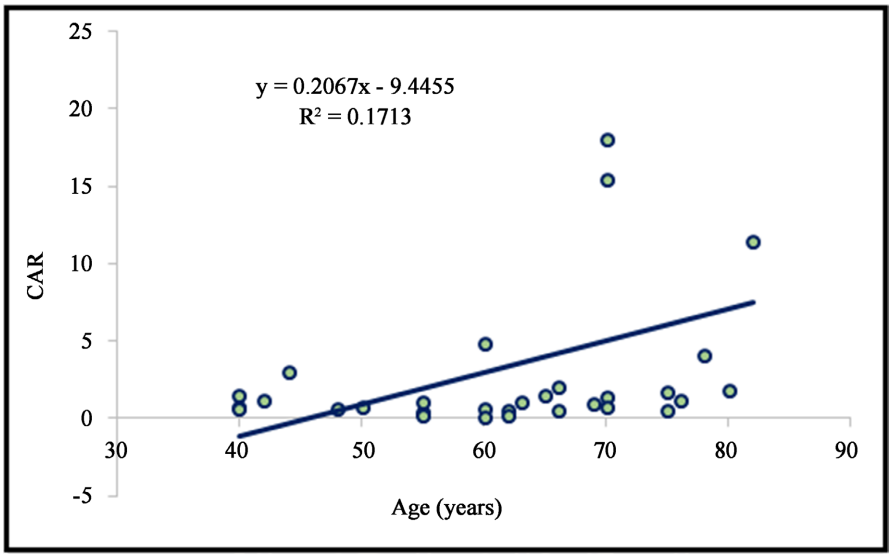

Figure 2. Correlation between CAR levels and age in group II according to scatter plot and regression line (P = 0.008, r = 0.459).

independent predictor for in-hospital MACEs, in agreement of Cagdas *et al.* who demonstrated this association also [7] and similarly Wei Wang *et al.* stated the same significance for in-hospital MACEs in patients with ACS [14].

It has been suggested that, as a novel inflammatory parameter, CAR is more sensitive and specific in the prediction of the systemic inflammatory state and prognosis in various cardiac and non-cardiac clinical conditions when compared with CRP and serum albumin separately [7] [14] [15] [16] [17].

CAR first was described by Fairclough *et al.* and proposed as a better prognostic parameter to predict poor prognosis than either serum CRP or albumin levels alone in patients with acute medical conditions [15]. There is increasing evidence that CAR is associated with poor prognosis in patients with tumors or sepsis [16] [18] [19] [20] [21] [22]. Previous reports, Karabağ *et al.*, have revealed that CAR can predict no-reflow in patients with ST-elevation myocardial infarction [23] and Zhang *et al.* concluded that the higher the CAR, the higher the risk of death in patients with ACS [24].

Acet *et al.* found that CAR was independently associated with the risk of MACE in STEMI patients undergoing primary percutaneous coronary intervention (pPCI) and adding CAR to the GRACE risk score system could increase the predictive value of GRACE score in the estimation of prognosis in STEMI patients undergoing PCI [25], and Kalyoncuoglu *et al.* concluded its usefulness in prediction of CAD severity in patients with NSTEMI and it may be a part of cardiovascular examination to identify individuals with NSTEMI at high risk for advanced CAD who might need a more aggressive therapeutic approach and closer clinical follow-up [26].

Furthermore, Wada *et al.* showed that the combination of serum albumin and hs-CRP as a marker is a stronger predictor than either marker alone in patients treated with percutaneous coronary intervention [27].

In this study, a remarkably worse short-term prognosis was observed in patients with serum hs-CRP levels > 4 mg/L, CRP > 5.25 mg/L. which are compatible with previous findings [28] [29]. It is most likely that CRP has a role in all phases of atherosclerosis by directly influencing processes such as endothelial damage, complement activation, apoptosis, vascular cell activation, and thrombosis [30].

There is also substantial evidence that decreased albumin plasma concentrations may be causally related to atherosclerosis development and progression [31] [32].

In the present study, heart failure development, arrhythmia and cardiogenic shock were the most important causes of MACE. This may be due to increased myocardial damage and decreased myocardial reserve, in agreement with Acet *et al.* [25].

An interesting finding regarding medical outcomes in this study considered a cut-off value of CAR (using hs-CRP and CRP) to be, 3.18 mg/L, 9.13 mg/L respectively, statistically significant in context of discrimination between medically treated ACS patients and death outcome in term of high CAR -which couldn't be

assessed by other authors up to our knowledge.

Similarly, a predictive cut-off value of CAR (using hs-CRP and CRP) had concluded to help in making management mode decision between conservative medical treatment from those indicated for immediate intervention PCI considering cut value of 1.4 mg/L and 0.78 mg/L respectively.

Another interesting finding in which there is a significant linear relationship between CAR (using hs-CRP) and duration of hospital stay-which may contributed to the development of complications and the need for further hospitalization. Moreover, there is significant linear relationship between CAR (using CRP) and age of the patients (P = 0.008, r = 459).

Therefore; it can be stated that CAR is a more valuable marker than each of CRP and albumin alone in the prediction of in hospital MACEs which is compatible with Cagdas *et al.* [7] Wei Wang *et al.* [14] reports, with good implication concerning the decision of early referral for interventional management rather than keeping with conservative medical management.

There were some limitations that ought to be considered like interfering factors with baseline measurement for both serum albumin and CRP patients' BMI and nutritional status in addition to the need of monitoring levels of both parameters in concern with patient recovery.

5. Conclusions

High CAR levels are associated with poor outcomes, as independent predictor for in-hospital MACEs, concerning ACS patient at presentation, as well as, it can be used as guide that helps in ascertaining the need for immediate interventional PCI rather than continuing conventional conservative medical treatment.

Accordingly, it can recommend estimation of CAR to identify patients with ACS at high risk for MACEs and to guide the decision for early medical intervention (PCI) that may be useful in CICU daily practice.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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