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IN-HOSPITAL OUTCOME OF ACUTE CORONARY SYNDROME PATIENTS WITH RAISED QUANTITATIVE C-REACTIVE PROTEIN LEVELS

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Abstract

Introduction: *CRP has been shown to reflect systemic and vascular inflammation and to predict future cardiovascular events. Elevated levels of CRP are associated with higher risk of adverse outcomes in patients at risk.*

Objectives: *To find the frequency of in-hospital outcomes of patients presenting with acute coronary syndrome and high serum CRP levels.*

Subjects & Methods: *This descriptive case series study conducted at the Cardiology Unit of Khyber Teaching Hospital, Peshawar, over a six-month period. 233 patients of 18-70 years of age and either gender who presented with confirmed diagnosed cases of ACS (i.e. presented with typical chest pain and diagnosed with STEMI, NSTEMI or unstable angina according to our operational definition) and CRP levels more than 6mg/dL at the time of presentation were included in the study. All the selected patients were observed for the clinical in-hospital outcome till their discharge as per defined in operational definition. SPSS software version 25.0 will be used for data entry and analysis purpose.*

Results. *73.4% (n=171) patients were males while rest of the patients were female. Cumulative mean age was 58.23 years ± 19.95 SD. Mean Troponin levels and CRP levels were noted as 2.01±0.63 ng/ml and 13.55±3.95 mg/L respectively. It was observed that 67.4% (n=157) were discharged with stable condition, whereas 9.9% (n=23) died. Heart failure was the most frequently observed in-hospital outcome 18.9% (n=44). Our study revealed that no statistically significant association (p-value≤0.05) was noticed only for any of the effect modifier except troponin levels and CRP levels.*

Conclusions*: Heart failure was noted as most frequent worst outcome followed by death and cardiogenic shock. No significant association was observed between in-hospital ACS outcomes and factors like ACS type, age, or gender. However, elevated CRP levels and troponin levels demonstrated statistically significant link to adverse in-hospital ACS outcomes.*

INTRODUCTION

Acute coronary syndrome (ACS) is a significant healthcare and economic challenge in low- to middle-income countries (LMICs). The incidence of ACS is increasing rapidly in these nations, resulting in approximately 7 million mortality and 129 million disability-adjusted life years each year.[i] The population of Southern Asia has been observed to have an elevated risk and an onset of ACS occurring 5-10 years sooner than that of the Western population. It is anticipated that in the near future, over 50 percent of the global burden of ACS will be shouldered by South Asian nations.[ii,iii] ACS encompasses the clinical manifestations of myocardial ischemia, including unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), typically resulting from the rupture of an atherosclerotic plaque and subsequent partial or complete occlusion of the infarct-related artery, leading to diminished coronary blood flow.[iv]

ACS arises from standard sterile inflammation, characterized by hyperglycemia, elevated levels of inflammatory cytokines, platelet activation, and leukocytosis. Inflammation is crucial in initiating and destabilizing atherosclerotic plaque.[v] Numerous inflammatory biomarkers have been employed as indicators of ACS. The majority of the investigations focused on C-reactive protein (CRP), fibrinogen, and interleukin-6 (IL-6).[vi] CRP is an acute phase reactant and a measure of systemic inflammation, serving as a relatively recent plasma indication for atherothrombotic illness.[vii] In recent years, CRP has emerged as an independent predictor of both short- and long-term outcomes in patients with acute myocardial infarction and has also been shown to influence the efficacy of reperfusion therapies for these individuals.[viii] Past few reports reflected that raised CRP is associated with increased risk of adverse events in patients with ACS.

Establishing the relationship between raised CRP levels and clinical outcomes in patients with ACS is of vital importance for the early detection of patients who are more vulnerable to the major adverse cardiovascular events (MACEs) such as myocardial infarction, cardiogenic shock or death. Its importance further increases in the low-resource healthcare settings, where there is an extreme need of cost-effective techniques for the prevention of MACEs in patients with ACS. It has been observed that geographic and ethnic variations affect the relationship of elevated CRP levels and clinical outcomes in ACS patients.[12,13] So, present study is planned to see the association of elevated CRP levels and clinical outcomes in ACS patients presenting to our setting. Our study results would be beneficial for clinicians to timely identify the patients at high risk of future MACEs and they would be able to devise strategies accordingly so that the outcome may be improved in these patients.

MATERIALS AND METHODS

The study utilized a descriptive case series design conducted at the Cardiology Unit of Khyber Teaching Hospital, Peshawar, over a six-month duration from March 20, 2022, to September 20, 2022. The sample size was calculated using the WHO sample size calculator for estimating population proportions, using parameters of a 95% confidence level, a 2%[10] anticipated proportion, and a 1.8% absolute precision, yielding a required sample of 233 persons. Patients were enrolled using a non-probability consecutive sampling method. The inclusion criteria included confirmed diagnosis of acute coronary syndrome (STEMI, NSTEMI, or unstable angina) with CRP levels >6 mg/dL at presentation, aged 18 to 70 years, irrespective of gender. Exclusion criteria disqualified patients with previous revascularization, valve replacement or repair, current infections, neoplastic disorders, chronic arthritis, or hepatic or renal insufficiency. Upon receiving ethical permission, suitable patients exhibiting characteristic of typical chest pain and fulfilling diagnostic criteria for acute coronary syndrome were enrolled after securing written informed consent. The principal investigator documented a thorough clinical history and conducted a physical examination. A senior phlebotomist aseptically collected 5ml blood samples for the investigation of troponin levels, CRP levels, complete blood count, and lipid profile, while ECGs were conducted for all subjects. Patients with increased CRP levels were monitored during their hospitalization to assess clinical outcomes. Demographic information and study results were meticulously documented on standardized collection

forms. Statistical analysis was conducted using SPSS version 25.0, with continuous data (age, CRP, and troponin levels) reported as mean±SD, and categorical variables (gender, ACS type, clinical outcomes) provided as frequencies and percentages. Potential confounding variables, including age, gender, ACS etiology, and biomarker levels, were controlled through stratification, followed by post-stratification analysis utilizing the chi-square test, with a p-value ≤0.05 deemed statistically significant.

RESULTS

We enrolled a total of two hundred and thirty-three (n=233) patients of either gender who were presented with ACS. ACS patient were categorized as STEMI, NSTEMI and unstable angina based on established criterion. Study population was male dominant (n=171; 73.4%). Mean age of total study patients calculated as 58.23 ± 9.95 years. Mean troponin levels and CRP levels were noted as 2.01±0.63 ng/ml and 13.55±3.95 mg/L respectively. Patients were distributed in different groups on the basis of age, Troponin levels and CRP levels. Based on the ACS etiology, it was noted that more than half (54%) of the patients were positive for STEMI (figure 1). Regarding in-hospital ACS outcomes among all the enrolled patients, it was observed that 67.4% (n=157) were discharged with stable condition, whereas 9.9% (n=23) died. Detailed patient distribution based on ACS etiology and in-hospital ACS outcomes is presented in figure 2. The study findings endorsed that there was statistically significant association between in-hospital ACS outcomes and Troponin levels (p-value = 0.000) and CRP levels (p-value = 0.000), as the p-value was less than 0.05. Contrary to this, no association was found between in-patient ACS outcomes and age (p-value = 0.565), gender (p-value = 0.129) and ACS etiology (p-value = 0.193). Findings of post stratification chi-square test for association in-hospital ACS outcomes and other variables are presented in Table 5, 6, 7, 8 and 9.

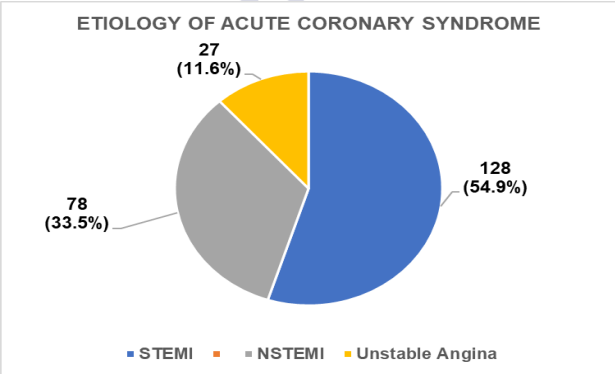

Table 1: Distribution of patients based on ACS etiology

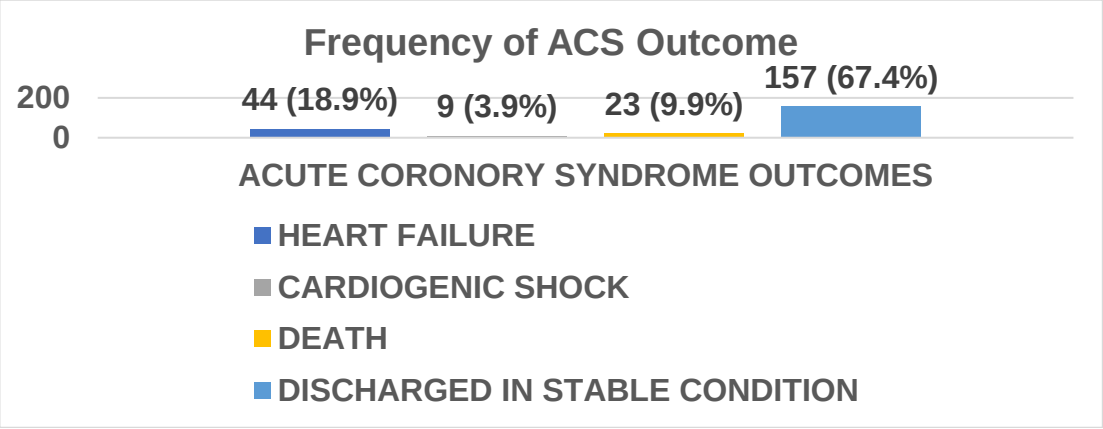

Figure 1: Distribution of patients based on in-hospital outcomes of ACS

Table 1: Findings of post stratification X^2 test for association between gender and ACS outcomes

Variable		Heart Failure n (%)	Cardiogenic Shock n (%)	Death n (%)	Discharged Stable n (%)	*p*-value
Gender	Male	35 (79.5%)	9 (100%)	18 (78.3%)	109 (69.4%)	0.129
	Female	9 (20.5%)	0 (0%)	5 (21.7%)	48 (30.6%)	
ACS Etiology	STEMI	22 (50%)	7 (77.8%)	9 (39.1%)	90 (57.3%)	0.193
	NSTEMI	18 (40.9%)	0 (0%)	10 (43.5%)	50 (31.8%)	
	Unstable Angina	4 (9.1%)	2 (22.2%)	4 (17.4%)	17 (10.8%)	
Age Groups	<50 years	10 (22.7%)	3 (33.3%)	5 (21.7%)	28 (17.8%)	0.565
	50-60 years	18 (40.9%)	4 (44.4%)	8 (34.8%)	51 (32.5%)	
	>60 years	16 (36.4%)	2 (22.2%)	10 (43.5%)	78 (49.7%)	
Troponin Levels	0.6-1.5 ng/mL	5 (11.4%)	2 (22.2%)	1 (4.3%)	49 (31.2%)	<0.001
	1.51-2.5 ng/mL	26 (59.1%)	7 (77.8%)	6 (26.1%)	82 (52.2%)	
	>2.5 ng/mL	13 (29.5%)	0 (0%)	16 (69.6%)	26 (16.6%)	
CRP Levels	6.1-10.0 mg/L	2 (4.5%)	0 (0%)	0 (0%)	39 (24.8%)	<0.001
	10.1-16.0 mg/L	31 (70.5%)	8 (88.9%)	10 (43.5%)	93 (59.2%)	
	>16.0 mg/L	11 (25%)	1 (11.1%)	13 (56.5%)	25 (15.9%)	

DISCUSSION

ACS poses a significant risk of serious consequences, including cardiogenic shock, heart failure, and mortality, rendering its prevention an essential public health objective. Significantly, low- and middle-income countries account for 80% of global ACS cases and 85% of associated morbidity.[ix] Recent researches linking elevated inflammatory markers to greater cardiovascular risk and CRP emerged as a most reliable inflammatory marker for evaluating risk in patients with ACS.[x] In low- and middle-income countries (LMICs), elevated mortality rates from ACS are exacerbated by insufficient pre-hospital emergency medical services, diagnostic and treatment delays, and inadequate healthcare coordination. Restricted access to specialized interventional cardiology and catheterization laboratories further diminishes the quality of care. It is advisable to monitor CRP levels in ACS patients and devise practical strategies. Furthermore, additional research that includes ethnic and geographic diversity is essential to enhance patient outcomes. [xi] In LMICs like Pakistan, data on elevated CRP levels and in-hospital outcomes for ACS patients is scarce. This study was conducted to fill this research gap and improve risk stratification. Results show that patients with increased CRP have lower in-hospital outcomes than those with normal CRP. These findings improve understanding of the ACS inflammatory response and may inform clinical management. Endorsing our study findings, several studies have corroborated a positive correlation between elevated CRP levels and adverse outcomes in ACS patients, including mortality. Umamaheshwari S, and colleagues reported that 77.27% (n=34/44) patients showed complications following ACS who were presented with raised CRP. Left ventricular failure was the most common complication in 22.7% (n=10/44) patients followed by cardiogenic shock and death in 18.18% (n=8/44) patients each.[xii] On the other hand, Liu Y et al in their study described that myocardial infarction and death were positive in 1.87% and 2.0% of patients who presented with elevated CRP levels. They further illustrated that 10.25% of patients with raised CRP levels required revascularization.[xiii]

Although, ACS affects both men and women, but presentation, risk factors, and results differ. This study's 73% male patient population matches global data demonstrating greater ACS prevalence among men in European (70%), Indian (76%), Tunisian

(79%), and Nepali (68%) populations. Men had more classic risk factors (smoking, diabetes, hyperlipidemia) and a family history of coronary artery disease, which may explain this gender gap. The cardioprotective effects of estrogen in women—which affects inflammation, endothelial function, and lipid metabolism—may also explain these disparities. These findings suggest male ACS patients need specific research and therapies to address risk factors.[xiv,xv,xvi,xvii] However, in our study, the relationship between patient gender and in-hospital outcomes among ACS patients with elevated CRP levels found to be non-significant. Parallel to this study, report from Sudan[xviii] and Middle eastern countries found no gender differences in in-hospital complications. By demonstrating the achievability of optimal in-hospital outcomes for both genders with appropriate management, this study acknowledged continued efforts to ensure equitable and evidence-based care for all ACS patients.

ACS can strike at any age, but research shows a significant increase in risk as people get older. The mean age of our study population was 58.23 years (SD ± 9.95 years). This finding aligns with observations from Brazilian (59.9 years) study.[xix] The risk of ACS is significantly elevated with advancing age, influenced by factors including tobacco use, diabetes mellitus, and dyslipidemia. Nevertheless, research from other parts of the world indicates an earlier onset of ACS with average ages of 38.28 years for males and 42.15 years for females. This younger demographic may be associated with genetic predispositions, familial history, and early arteriosclerosis.[xx]

The impact of age on in-hospital outcomes for patients with ACS is a complex issue. In this study, no significant association was found between age and in-hospital ACS outcomes. Similarly, a growing body of research suggests that timely diagnosis, coupled with effective interventions like PCI and optimized medication regimens, can potentially diminish the influence of age as determinant of in-hospital mortality and complications in ACS patients.[xxi] Conversely, some studies have identified a positive association between older age and adverse outcomes, including a higher incidence of complications, prolonged hospitalizations, and increased mortality.[xxii,xxiii] These contrasting findings might be attributed to the cumulative burden of co-morbidities frequently observed in older ACS patient. Furthermore these are relatively older studies. Age-related physiological alterations, including diminished cardiac reserve and blunted responsiveness to medications, may worsen outcomes in elderly patients.[xxiv,xxv]

The severity of ACS dictates its classification, which spans from less severe NSTEMI to critical STEMI, with UA positioned as intermediate. This study identified a STEMI prevalence of 55%, consistent with regional trends, likely attributable to risk factors such as dyslipidemia, hypertension, diabetes, smoking, and obesity. Conversely, Western studies indicate a greater frequency of NSTEMI, ascribed to aging populations and chronic comorbidities that exacerbate endothelial dysfunction.[xxvi,xxvii]

Among many in-hospital outcomes of ACS, the death rate in this study was 9.9%. This mortality rate falls within the documented range observed in other studies on ACS. Reports from Iran, Turkey, Pakistan and Sri-lanka documented a similar mortality rate of 7.1%, 11.1%, 11.7% and 12.3%, respectively.[xxviii,xxix] Whereas, Ethiopian studies reported higher mortality rates of 24.5% and 27.4%.[xxx] By acknowledging the observed range across different settings, it emphasizes the variability of healthcare quality and ongoing efforts to optimize ACS management and outcomes worldwide.

This study found also found significant statistical association between troponin levels and in-hospital ACS outcomes, which accords with studies from Middle east and USA.[xxxi,xxxii] Elevated troponin levels frequently coincide with more extensive myocardial infarction and a decline in left ventricular function. These factors are known to be significant determinants of in-hospital outcomes in ACS patients, including mortality and complications arising from heart failure. On the contrary, few studies have found no statistically significant association.[xxxiii] This discordance might be attributable to variations in several factors, including the sensitivity of troponin assays, the timing of blood draws for measurement, and the specific subtypes of ACS that were included in each study. In addition, pre-existing chronic kidney disease and co-morbidities that affect troponin clearance can lead to untrue elevations, potentially obscuring the true relationship between troponin levels and ACS outcomes.

According to the findings of this study, there held a significant association between CRP levels and outcomes in patients with ACS. This finding was in line with a plethora of studies depicting association of elevated CRP levels with the severity of ACS and predicted worse long-term outcomes, including major cardiovascular events and mortality. These results encourage CRP as a potential indicator of the underlying inflammatory milieu associated with atherosclerotic plaque disruption and subsequent myocardial damage in ACS patients. However, studies conducted in healthcare settings like Egypt and Pakistan did not observe association between in-hospital outcomes and CRP levels. This suggests that relationship between CRP and ACS outcomes is potentially influenced by various unidentified factors. The observed disparity could potentially stem from methodological heterogeneities, including variations in sample size, the specific ACS subtypes investigated, and CRP measurement. Additionally, CRP levels can be confounded by factors like pre-existing inflammatory conditions or infections, ultimately resulting in misinterpretations.

This study of ACS patients offers a commendable attempt to shed light on this prevalent cardiovascular condition. The study's prospective nature stands as a significant strength. By enrolling patients upon admission, it established a clearer temporal relationship between variables, strengthening the observed associations. However, the limitations inherent to this design warranted careful consideration. The relatively small sample size of patients restricted the study's statistical power. This limitation might have obscured the detection of potentially important, yet subtle, associations, particularly regarding age and gender. Furthermore, the generalizability of the findings was restricted by the single-center design. Patient demographics, disease severity, and treatment protocols can vary considerably across institutions, limiting the applicability of the observed relationships to a broader ACS population. The possibility of selection bias also merits mention. The study population might have not accurately reflected the entire spectrum of ACS presentations and potential confounding variables at the center. Given the aforementioned limitations, future research efforts should prioritize multi-center studies with larger, more diverse populations and longer-term outcome assessments to solidify our understanding of ACS and refine treatment strategies across various patient subgroups.

CONCLUSIONS

The findings of our study revealed a predominance of males and a higher prevalence of STEMI presentations. Heart failure was noted as most frequent worst outcome followed by death and cardiogenic shock. No significant association was observed between in-hospital ACS outcomes and factors like ACS type, age, or gender. However, elevated CRP levels and troponin levels demonstrated statistically significant link to adverse in-hospital ACS outcomes. This finding aligns with significant role of high CRP levels as an inflammatory marker, potentially highlighting the influence of inflammation on ACS severity and outcomes.

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