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Predictors of In-Hospital Mortality in Patients with Acute Coronary Syndrome Referred from Non-Cardiology Clinics: A Comparison Between Medical Therapy and Percutaneous Coronary Intervention

Kardiyoloji Dışı Kliniklerden Akut Koroner Sendrom İle Konsülte Edilen Hastalarda Hastane İçi Mortalite Öngördürücüleri: Tıbbi Tedavi Ve Perkütan Koroner Girişim Arasında Bir Karşılaştırma

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Öz

Akut koroner sendrom hastalarının, acil servise veya koroner yoğun bakım ünitesine doğrudan kabul edilenlere kıyasla, kardiyoloji dışı kliniklerde tedavi yönetimi daha zorlu olabilmektedir. Bu çalışmanın amacı, kardiyoloji dışı kliniklerde yatan akut koroner sendrom hastalarındaki hastane içi mortalite öngördürücülerini araştırmak ve sadece tıbbi tedavi ile veya ek olarak perkütan koroner girişim ile yönetilen hastalar arasındaki sonuçları karşılaştırmaktı. Bu retrospektif bir çalışmaydı. Ocak 2018 - Aralık 2023 arasında kardiyoloji dışı kliniklerden akut koroner sendrom olarak konsülte edilen hastalar (ST elevasyonlu miyokart enfarktüslü hastalar hariç) çalışmaya dahil edildi. Hastalar, tedavi yönetimine göre iki gruba ayrıldı: yalnızca tıbbi tedavi alanlar ve medikal tedaviye ek olarak koroner anjiyografi yapılanlar. Hastane içi mortalite açısından bağımsız öngördürücüler, ikili lojistik regresyon analizi kullanılarak belirlendi. Çalışmaya toplam 241 hasta dahil edildi. 112 hasta (%46.4) yalnızca tıbbi tedavi aldı (Grup 1), 129 hastaya (%53.6) koroner anjiyografi yapıldı (Grup 2) ve Grup 2'deki 69 hastaya perkütan koroner girişim uygulandı. Alt grup analizi, başlangıçtan itibaren medikal tedavi alan hastaların, perkütan koroner girişim uygulanan hastalara göre daha yüksek hastanede ölüm oranına sahip olduğunu gösterdi; medikal tedavi alan 172 hastadan 32'si (%18.6), perkütan koroner girişim uygulanan 69 hastadan 10'unda (%14.4) mortalite gelişti (p=0.040). İleri yaş, düşük serum albumin, yüksek bilirubin, üre ve kardiyak troponin seviyeleri ile COVID-19 enfeksiyonu artmış hastane içi mortalite ile ilişkili bulunurken, kardiyoloji dışı kliniklerden konsülte edilen akut koroner sendrom hastalarında perkütan koroner girişim, tek başına azalmış hastane içi mortalite ile ilişkiliydi.

Anahtar Kelimeler: Akut Koroner Sendrom, Mortalite, Perkütan Koroner Girişim

Abstract

The management of patients with acute coronary syndrome who are hospitalized in non-cardiology clinics can be more challenging compared to those admitted directly to the emergency department or coronary intensive care unit. The aim of this study was to investigate the predictors of in-hospital mortality in patients with acute coronary syndrome who were initially hospitalized in non-cardiology clinics, and to compare outcomes between those managed with medical therapy alone versus those who also underwent percutaneous coronary intervention. This was a retrospective study. We enrolled patients who were referred as acute coronary syndrome from non-cardiology clinics (excluding patients with ST elevation myocardial infarction) between January 2018 and December 2023. Patients were divided into two groups based on their management approach: those who received medical therapy only and those who also underwent coronary angiography. Independent predictors of in-hospital mortality were identified using binary logistic regression analysis. A total of 241 patients were included in this study. While 112 patients (46.4%) received medical therapy only (Group 1), 129 patients (53.6%) underwent coronary angiography (Group 2), and 69 of 129 patients underwent percutaneous coronary intervention. The subgroup analysis showed that patients receiving medical therapy from the onset after coronary angiography (CAG) had a higher in-hospital mortality rate (32 of 172 patients, 18.6%) than those undergoing percutaneous coronary intervention (PCI) (10 of 69 patients, 14.4%), with a p-value of 0.040. We found that while advanced age, low serum albumin, elevated bilirubin, blood urea nitrogen, and cardiac troponin levels, as well as COVID-19 infection were associated with increased in-hospital mortality; percutaneous coronary intervention was associated with reduced in-hospital mortality in patients with acute coronary syndrome who were referred from non-cardiology clinics.

Keywords: Acute Coronary Syndrome, Mortality, Percutaneous Coronary Intervention

Introduction

The diagnosis of acute coronary syndrome (ACS) requires an elevation of cardiac troponin levels, and consultations from other clinics with suspicion of ACS always include this parameter. However, we are aware that various clinical conditions may lead to an increase in troponin levels (in the absence of coronary obstruction), such as ischemic or hemorrhagic cerebrovascular events, renal failure, severe infections causing sepsis, acidosis, extreme anemia, etc. Therefore, an additional finding related to cardiac ischemia (such as ischemic electrocardiographic or echocardiographic findings, ischemic symptoms, etc.) recommended in clinical guidelines is necessary (1). Managing patients with suspicion of ACS in the emergency department or outpatient clinic of cardiology is relatively straightforward for

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a cardiologist. However, in clinics outside of cardiology, patients referred with suspicion of ACS often have multiple comorbidities that can impact our assessment and final decision. Current guidelines may not cover all scenarios for this specific population.

For example, when a patient hospitalized for an ischemic stroke event is referred from a neurology critical care unit with a high level of high-sensitive troponin T (hs-TnT), it is necessary to differentiate whether this elevation is due to acute coronary syndrome (ACS) or stroke. Patients with acute ischemic stroke and myocardial infarction share similar risk factors, leading to a high risk for subsequent ACS in stroke patients and vice versa (2). Up to 60% of ischemic stroke patients exhibit hs-TnT levels above the upper reference limit for defining myocardial injury. Diagnosing ACS becomes more challenging when other parameters, such as ECG or echocardiographic findings, are normal, especially in patients who are unable to communicate their symptoms (e.g., intubated). Furthermore, the addition of heparin to medical therapy for ACS increases the risk of hemorrhagic transformation of vulnerable ischemic brain tissue in this specific population. In conclusion, the diagnosis and therapeutic decision-making for such patients are complex and critical.

Patients at other clinics, such as surgery departments (referred in the perioperative period), gastroenterology (e.g., a patient with massive gastrointestinal bleeding), nephrology (e.g., a patient with atypical chest pain during hemodialysis and elevated hs-TnT level), and the anesthesiology intensive care unit (e.g., an intubated patient with metabolic acidosis, lobar pneumonia, and elevated hs-TnT level), should also be carefully evaluated for the final decision. When a patient's diagnosis is accepted as ACS (only unstable angina or non-ST elevation myocardial infarction for this study), they need to be treated medically or undergo percutaneous coronary intervention (PCI).

In this study, we aimed to determine the predictors of in-hospital mortality for high-risk patients diagnosed with ACS at non-cardiology clinics who were managed medically and/or underwent coronary angiography with/without PCI.

Material and Method

Study Design

This was a retrospective single-center study. This study was carried out in accordance with the conditions of the declaration of Helsinki and approved by our local ethical committee.

Study Population

We enrolled patients who were referred as acute coronary syndrome from non-cardiology clinics (excluding patients with ST elevation myocardial infarction) between January 2018 and December 2023. Patients with relative contraindications to CAG (e.g., septic shock, active gastrointestinal bleeding), patients who refused coronary intervention or had a lack of recorded data, those with excessive exposure to contrast media (>500 mL) during percutaneous intervention, acute liver failure, recent hemorrhagic stroke (within 15 days), thyrotoxicosis, and patients who underwent coronary artery bypass surgery as a result of CAG (including ≥ 50% stenosis of the left main coronary artery) were excluded from the study. We analyzed digitally recorded data for demographic characteristics, risk factors, comorbidities, laboratory and echocardiographic findings, angiography findings and amount of contrast media, medications, and primary diagnosis of patients. We divided the patients into two groups: those who received medical therapy only (Group 1, n=112) and those who underwent coronary angiography in addition to medical therapy (Group 2, n=129). To determine the independent effect of interventional treatment and other possible factors on mortality, the study population was analyzed by dividing it into two subgroups: patients who survived (n=199) and those who experienced in-hospital exitus (n=42).

Coronary Angiography, Monitorization and Further Management

All coronary angiography procedures were performed via the femoral or radial (mostly radial) approach. Patients with non-ST elevation myocardial infarction (NSTEMI) or unstable angina (UA) pectoris underwent coronary angiography within 24 hours after diagnosis, according to the recommendations of recent guidelines (3). We used the Global Registry of Acute Coronary Events (GRACE) score to identify the risk category of patients, and the result of the score was one of the main factors in decision-making for our therapeutic choice (4). We used a non-ionic and low-osmolality contrast agent (Optiray© [Ioversol]) and administered it manually to all patients in our institution, and the amount of contrast media used was obtained from the digitally recorded data at the end of each intervention. All patients received acetylsalicylic acid and ticagrelor or clopidogrel, high-dose statin, heparin (before and during PCI), a beta-blocker (if possible), and an angiotensin-converting enzyme inhibitor (if possible). The second antiplatelet agent was loaded when it was decided to perform PCI. In cases where percutaneous coronary intervention (PCI) was deemed necessary, we used drug-eluting stents for all patients. The choice of stent size and type was based on the characteristics of the lesion and the vessel size. In cases where the lesion was considered complex or calcified (e.g. left main coronary lesions), we used intravascular ultrasound (IVUS) to guide our intervention.

We closely monitored all patients during the procedure for any signs of complications such as contrast-associated acute kidney injury (CA-AKI), hypotension, or arrhythmias. Immediate complications were managed promptly according to established protocols in our institution.

After the procedure, all patients were transferred to the coronary care unit for further monitoring and management. We provided detailed instructions to patients regarding their medications, lifestyle modifications, and follow-up appointments.

Overall, our approach to coronary angiography and PCI in patients with NSTEMI or UA pectoris was guided by evidence-based guidelines and individual patient characteristics. Our goal was to provide timely and effective treatment to improve outcomes and reduce the risk of future cardiovascular events.

Statistical Analysis

SPSS 21.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was applied to the variables to determine whether or not they were normally distributed. Categorical variables were presented as number and percentage, and all continuous variables were presented as median and percentiles due to the non-parametric distribution. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, as appropriate.

Table 1. Baseline characteristics of Group 1 and 2.

Parameter	Group 1 (n = 112)	Group 2 (n = 129)	p value
Age (years)	70 (61.5 - 73.5)	71.0 (64.5 - 81.0)	0.052
Gender (female), n (%)	46 (41.1)	58 (44.9)	0.058
Heart rate (bpm)	86 (58 - 116)	89 (54 - 121)	0.074
SBP (mmHg)	126.8 (95.6 - 148.8)	123.5 (92.6 - 145.9)	0.158
BMI (kg/m^2)	24.4 (19.6 - 28.8)	23.8 (19.1 - 27.6)	0.452
Smoking, n (%)	31 (27.6)	42 (32.5)	0.126
Hypertension, n (%)	72 (64.3)	83 (64.4)	0.993
Diabetes mellitus, n (%)	54 (48.2)	70 (54.2)	**0.044**
Dyslipidemia, n (%)	45 (40.1)	58 (44.9)	0.096
History of CHD, n (%)	15 (13.3)	18 (13.9)	0.882
Ejection fraction (%)	50.5 (42.5 - 55.0)	45.5 (40.5 - 50.5)	**0.008**
GRACE score	112.3 (82.5 - 131.8)	132.7 (94.4 - 168.4)	**0.004**
Glucose (mg/dl)	147.0 (112.0 - 196.0)	134.0 (100.5 - 214.5)	0.546
BUN (mg/dl)	89.0 (55.5 - 127.0)	61.5 (36.5 - 100.0)	**< 0.001**
Creatinine (mg/dl)	1.5 (1.2 - 2.6)	1.3 (0.9 - 2.7)	0.055
AST (U/L)	41.0 (26.0 - 78.0)	34.0 (20.0 - 76.0)	0.081
ALT (U/L)	30.0 (16.0 - 54.0)	26.0 (18.0 - 46.0)	0.485
Sodium (mEq/L)	137.0 (134.0 - 140.0)	136.0 (134.0 - 139.0)	0.207
Potassium (mmol/L)	4.3 (3.8 - 4.7)	4.2 (3.8 - 4.6)	0.433
Albumin (g/dl)	2.8 (2.2 - 3.1)	3.1 (2.8 - 3.5)	**< 0.001**
Total Bilirubin (mg/dl)	0.6 (0.4 - 1.1)	0.5 (0.4 - 1.0)	0.180
CRP (mg/dl)	108.0 (55.0 - 172.0)	66.0 (19.5 - 179.5)	**0.001**
Troponin (ng/L)	24.5 (11.5 - 120.0)	58.0 (21.0 - 143.0)	**0.024**
Hemoglobin (g/dl)	9.6 (8.2 - 11.6)	10.1 (8.8 - 11.7)	0.160
Hematocrit (%)	29.0 (24.0 - 33.5)	30.0 (26.5 - 34.0)	0.082
WBC (×10^9/L)	11.8 (8.2 - 16.8)	10.1 (8.1 - 15.4)	0.339
Platelet (×10^6/L)	221.0 (153.0 - 312.0)	236.5 (166.5 - 299.5)	0.414
Infection, n (%)	18 (16.1)	28 (21.7)	0.060
Covid-19, n (%)	14 (12.5)	36 (27.9)	**0.018**
AKI, n (%)	14 (12.5)	16 (12.4)	0.980
GI bleeding, n (%)	4 (3.6)	5 (3.4)	0.898
Stroke, n (%)	7 (4.7)	7 (5.4)	0.504
Postoperative, n (%)	12 (10.7)	12 (9.3)	0.466
DKA/HHNC, n (%)	3 (2.7)	4 (3.1)	0.920
Duration of Hospitalization (day)	8.3 (4.6 - 11.8)	7.5 (4.5 - 10.5)	**0.008**
Amount of CM (ml)		32.5 (24.5 - 84.0)	
CA-AKI, n (%)		2 (1.5)	
Medications			
Antiplatelet	22 (14.7)	16 (12.4)	0.541
Oral Anticoagulant	8 (5.3)	5 (3.8)	0.125

AKI; acute kidney injury, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BUN; blood urea nitrogen, CRP; C-reactive protein, DKA; diabetic ketoacidosis, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, hs; high-sensitive, SBP; systolic blood pressure, WBC; white blood cell

The Mann-Whitney U test was used to compare parameters that were not normally distributed. We performed binary logistic regression analysis to determine the independent predictors of in-hospital mortality after eliminating one of the parameters that showed a significant correlation with each other. Therefore, we performed two regression models in a stepwise fashion with a forward likelihood model;

one of them included the CAG status, and the other one included the intervention status as a categorical variable. Pairs such as urea-creatinine and hemoglobin-hematocrit, which were found to have a significant linear correlation, were also analyzed separately. We presented the results of the variables that were significantly related to in-hospital mortality. We conducted a prior power analysis based on the average results obtained from the in-hospital mortality data of randomized studies comparing conservative and invasive treatments in patients with acute coronary syndrome over the past decade. The calculated sample size, effect size, type I error probability, and power values we obtained are as follows: 242, 0.362, 0.05 and 0.80. When compared to our sample size calculation, one group had 9 fewer patients, while the other group had 8 more patients. Therefore, a post-hoc power analysis was also conducted based on the number of patients included in the study and the average of composite endpoint incidences. The calculated *Cohen's h* value found to be 0.118 and power value was found to be 0.974. All statistical testing was based on a 2-sided $\alpha = 0.05$ significance level.

Table 2. Comparison of baseline characteristics between patients who survived and those who died during the in-hospital period.

Parameter	Survived (n = 199)	Exitus (n = 42)	p value
Age (years)	68.5 (60.0 – 73.5)	72.0 (62.5 – 81.5)	**0.030**
Gender (female), n (%)	86 (43.2)	18 (42.8)	0.864
Heart Rate (bpm)	82 (59-118)	85 (50 - 126)	0.150
SBP (mmHg)	122 (94.0 – 135.0)	118 (91.0 - 130.0)	0.086
BMI (kg/m^2)	23.8 (18.9- 27.5)	25.1 (19.3 - 29.7)	0.258
Smoking, n (%)	60 (30.1)	13 (30.9)	0.820
Hypertension, n (%)	128 (64.3)	27 (64.2)	0.952
Diabetes Mellitus, n (%)	102 (51.2)	22 (52.3)	0.285
Dyslipidemia, n (%)	85 (42.7)	18 (42.9)	0.950
History of CHD, n (%)	27 (13.5)	6 (14.2)	0.290
Ejection Fraction (%)	51.0 (46.0 - 56.0)	49.0 (44.5 - 55.5)	0.098
GRACE score	111.0 (88.0 - 135.0)	138.5 (105.5 - 172.3)	**0.001**
Glucose (mg/dL)	129.0 (108.0 - 175.0)	132.5 (97.0 - 218.0)	0.110
BUN (mg/dl)	58.0 (42.0 - 96.0)	78.50 (52.0 - 122.0)	**0.002**
Creatinine (mg/dl)	1.19 (1.02 - 1.90)	1.38 (1.10 - 2.22)	**0.035**
AST (U/L)	41.0 (22.5 - 86.0)	45.5 (23.5 - 78.5)	0.060
ALT (U/L)	24.5 (18.5 – 54.0)	27.5 (19.0 - 53.5)	0.345
Sodium (mEq/L)	132.5 (128.5 - 136.0)	134.0 (130.5 - 139.5)	0.186
Potassium (mmol/L)	4.3 (3.7 - 4.9)	4.2 (3.8 - 4.8)	0.660
Albumin (g/dL)	3.8 (2.8 - 4.4)	2.2 (1.9 - 3.0)	**< 0.001**
Total Bilirubin (mg/dL)	0.42 (0.31 - 1.0)	0.95 (0.55 - 1.80)	**0.002**
CRP (mg/dL)	64.0 (42.0 - 105.5)	72.5 (48.5 - 124.5)	**0.040**
Troponin (ng/L)	42.0 (28.0 - 110.0)	58.5 (35.0 - 139.5)	**0.003**
Hemoglobin (g/dL)	10.9 (9.2 – 12.8)	10.2 (8.4 - 11.6)	0.550
Hematocrit (%)	29.4 (26.5 – 35.4)	28.8 (25.1 - 33.2)	0.332
WBC ($\times 10^9$/L)	10.2 (8.4 - 15.4)	11.4 (8.9 - 18.5)	0.184
Platelet ($\times 10^6$/L)	228.5 (161.0 - 315.0)	230.0 (162.5 - 321.0)	0.640
Infection, n (%)	38 (19.1)	8 (19.0)	0.896
COVID-19, n (%)	35 (17.6)	15 (35.7)	**< 0.001**
AKI, n (%)	25 (12.5)	5 (11.9)	0.285
GI bleeding, n (%)	8 (4.0)	1 (2.4)	0.089
Stroke, n (%)	11 (5.5)	3 (4.8)	0.072
Postoperative, n (%)	20 (10.0)	4 (9.5)	0.788
DKA/HHNC, n (%)	6 (3.0)	1 (2.4)	0.115
PCI	59 (29.6)	10 (23.8)	**0.001**

AKI; acute kidney injury, ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, BUN; blood urea nitrogen, CHD; coronary heart disease, CRP; C-reactive protein, DKA; diabetic ketoacidosis, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, hs; high-sensitive, PCI; percutaneous coronary intervention, SBP; systolic blood pressure, WBC; white blood cell.

Results

A total of 241 patients were included in this study. While 112 patients (46.4%) received medical therapy only (Group 1), 129 patients (53.6%) underwent CAG (Group 2). The median age (70 [61.5 - 73.5] vs 71 [64.5 - 81.0], p=0.052) and sex (female patients; n=46 [41.1] vs n=58 [44.9], p=0.058) distribution for Group 1 and 2 were similar. All parameters (laboratory findings including troponin level, primary diagnosis of patients, risk factors such as hypertension and diabetes mellitus, ejection fraction, amount of contrast media, and contrast-associated acute kidney injury percentages) in addition to the demographic characteristics of patients were presented in Tables 1 and 2.

Upon analyzing the results based on whether patients underwent coronary angiography (CAG), we found significant differences in ejection fraction (EF),

serum BUN, albumin, CRP, and troponin levels, as well as the prevalence of diabetes mellitus (DM) and COVID-19 infection between the two groups (Group 1 and Group 2) (Table 1). The number of patients who underwent PCI was significantly higher in the group of participants who survived compared to those who did not (59 of 199 patients [29.6%] vs 10 of 42 patients [23.8%], p=0.001) (Table 2). The subgroup analysis of in-hospital mortality indicated that patients receiving medical therapy from the onset and as a result of CAG had a significantly higher mortality rate (32 of 172 patients, 18.6%) compared to those who underwent PCI (10 of 69 patients, 14.4%), with a p-value of 0.040.

Table 3. The results of binary logistic regression analysis.

		95% CI of OR's		
Parameters (reference category)	**Odds Ratio**	**Lower**	**Upper**	**p value**
Age	1,15	1,011	1,091	**0.006**
Gender (female)	0,89	0,375	2,113	0.791
HT (-)	0,863	0,346	2,156	0.752
DM (-)	0,952	0,408	2,226	0.910
PCI (-)	0,095	0,036	0,249	**< 0.001**
Infection (-)	1,435	0,413	4,985	0.570
COVID-19 (-)	2,01	1,425	4,615	**0.012**
EF	0,975	0,901	1,21	0.286
BUN	1,18	1,08	1,218	**0.001**
Albumin	0,16	0,063	0,407	**< 0.001**
Bilirubin	2,207	1,409	3,455	**< 0.001**
CRP	0,997	0,993	1,002	0.237
Hemoglobin	0,973	0,788	1,202	0.800
WBC	1,007	0,989	1,026	0.449
AKI (-)	0,783	0,245	2,504	0.680
GI bleeding (-)	0,303	0,036	2,534	0.270
Stroke (-)	0,168	0,021	1,365	0.095
Postoperative (-)	0,861	0,234	3,174	0.882
DKA/HHNC (-)	0,577	0,035	4,476	0.700
Troponin	1,641	1,18	2,282	**< 0.001**

*The p-value of the model's Hosmer-Lemeshow test was found to be 0.23", AKI; acute kidney injury, BUN; blood urea nitrogen, CRP; C-reactive protein, DKA; diabetic ketoacidosis, DM; diabetes mellitus, EF; ejection fraction, GI; gastro-intestinal, HHNC; hyperglycemic hyperosmolar non-ketotic coma, HT; hypertension, PCI; percutaneous coronary intervention, WBC; white blood cell., Dependent variable: In-hospital Mortality

The study population was also compared based on whether in-hospital mortality occurred. While age, GRACE score, the number of patients with Covid-19, BUN, creatinin, total bilirubin, and troponin levels were significantly higher in patints who died during in-hospital period; serum albumin level was significantly higher in patient who survived (Table 2). The number of patients who underwent PCI was significantly higher in the group of participants who survived compared to those who did not (Table 2).

All percutaneous interventions were successful, and no major complications were recorded. The incidence of contrast-associated acute kidney injury (CA-AKI) was 1.5% (n=2) in Group 2 and 17.3% (n=12) in patients who further underwent PCI; however, none of them required hemodialysis, and their renal functions returned to the normal range during the in-hospital period. We observed exitus in only 1 of the 14 cases with CA-AKI; therefore, we did not include this parameter in the regression analysis.

We also took possible confounders into account in terms of being predictors of in-hospital mortality. The binary logistic regression models revealed that advanced age, elevated total bilirubin, BUN, and troponin levels, decreased serum albumin, and the presence of COVID-19 infection were significant predictors of in-hospital mortality (Figure 1 and Table 3). After adjusting for all confounders, the analysis showed that PCI and elevated serum albumin levels were significantly associated with lower in-hospital mortality (Figure 1 and Table 3). Serum creatinine levels (data not shown due to a separate regression analysis correlating with BUN) and CRP levels (see Figure 1 and Table 3) were found to have no significant relationship with in-hospital mortality.

Discussion

Predicting in-hospital mortality for high-risk patients with acute coronary syndrome (ACS) is crucial for improving patient outcomes. Comparing outcomes between patients who received medical therapy only and those who underwent PCI can provide valuable insights into the effectiveness of different treatment approaches. Several randomized controlled trials and meta-analyses of many randomized trials have evaluated conservative versus invasive approaches, and they supported an early invasive strategy for patients who are at moderate to high risk (5).

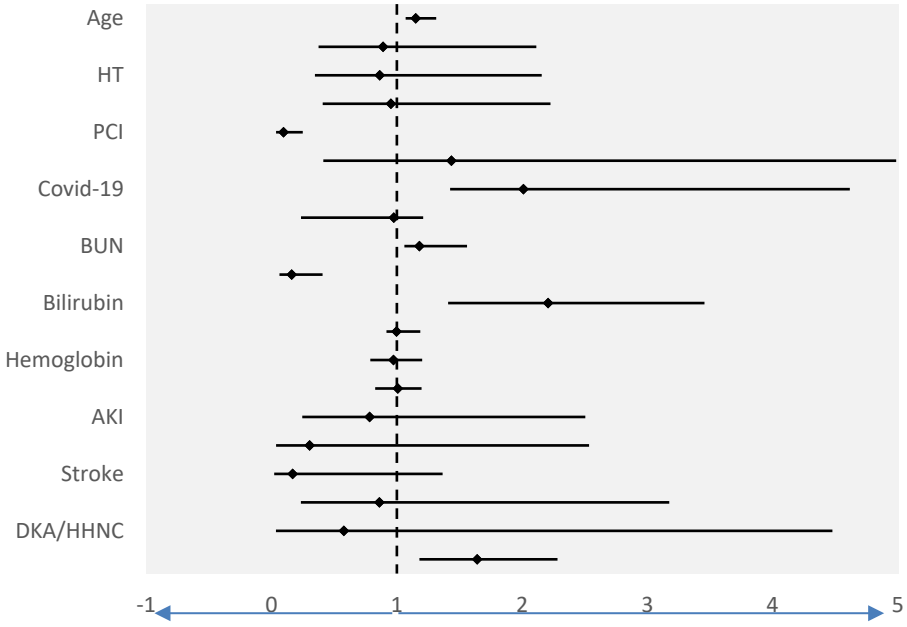

Figure 1. Forest plot graphic for possible predictors of in-hospital mortality.

We found that in-hospital mortality was significantly lower in the PCI group, although the number of patients managed conservatively was higher compared to the invasive management group due to the high-risk factors of our study patients (such as active infection, hemodynamic instability, frailty, recent stroke, etc.). The remaining patients who had no such risk factors and received only medical therapy were at relatively low risk according to the GRACE score. After adjusting for key covariates, we identified serum albumin levels as having a negative relationship with in-hospital mortality, while BUN, bilirubin, and troponin levels were positively associated with increased mortality.

A meta-analysis showed that serum albumin level is an independent predictor of all-cause mortality (risk ratio [RR] 2.15; 95% confidence interval [CI] 1.68 - 2.75) in patients with ACS (6). However, clinical trials could not demonstrate that correcting serum albumin level by intravenous infusion decreases the mortality rate in ACS patients. It was also shown in a study that serum albumin (< 3.65 mg/dL) at admission was an independent predictor of high SYNTAX score (odds ratio 4.329, 95% confidence interval 2.028 - 8.264; $p < 0.001$) and in-hospital all-cause mortality in patients with ACS (7). Another clinical trial demonstrated that serum albumin level ≤ 3.50 g/dl was an independent predictor of new-onset heart failure and in-hospital mortality in this patient group (8). The inflammatory state may be speculated as an underlying mechanism for hypoalbuminemia in this clinical setting. Hypoalbuminemia was linked with increased oxidative stress, platelet activation and aggregation, which triggered thrombotic events; moreover, low albumin level can result in decreased formation of lipoxins, resolvins and protectins, tilting the balance more toward pro-inflammatory events, leading to an increased risk of death for the critically ill (9,10).

Another marker we found to be linked with increased in-hospital mortality in our study population was BUN level. Kirtane et al. (11) found that among patients with ACS and normal to mildly reduced glomerular filtration rate (GFR), an elevated BUN was associated with increased mortality independent of other biomarkers. An elevated BUN may reflect a state of renal hypoperfusion due to hypovolemia, renovascular disease, or reduced cardiac output. In these states, BUN may rise independent of a change in GFR or serum creatinin due to enhanced urea reabsorption under activation of the sympathetic nervous and renin-angiotensin-aldosterone systems (12). This may be of particular relevance in patients with milder reductions in glomerular filtration rate. Another prospective study showed that patients with BUN > 32.5mg/dl were almost 20 times more likely to be associated with mortality as compared to reference group (13).

The other marker which we found to be related to mortality was total bilirubin. In a meta-analysis it was shown that elevated serum total bilirubin level was significantly positively associated with in-hospital cardiovascular death and MACE in patients with ACS (14). Bilirubin is an endogenous antioxidant, which resists the oxidative modification of low-density lipoprotein cholesterol, participates in scavenging oxygen-free radicals, and increases

heme oxygenase activity and the ability of serum cholesterol to dissolve. The level of bilirubin increased transiently in the acute phase of AMI and returned to the normal instantly, and initial serum bilirubin levels may reflect the severity of acute myocardial damage (15). In our study serum bilirubin levels were measured at the time of the diagnosis of ACS; therefore, this might be a coincidental finding.

Lastly, and not surprisingly, elevated serum troponin level was an independent predictor of mortality in our study, which is a well-known fact in the literature.

We also included primary diagnoses of the study population into the binary logistic regression analysis to see whether a specific comorbidity was related to in-hospital mortality or not. None of the diagnoses were significantly related to in-hospital mortality, except Covid-19 infection. In a recent trial, it was shown that gastrointestinal bleeding was not related to in-hospital mortality in patients with acute cardiovascular diseases; however, it was an independent risk factor for subsequent cardiovascular events (16). Another study revealed that PCI is safe in patients with recent ischemic stroke, and showed that the primary endpoints (composite of death, recurrent MI, coronary re-intervention, recurrent stroke, or bleeding during 1-year follow-up) were not enhanced in the PCI arm compared to the medical therapy arm (17). In a recent trial, it was shown that in-hospital mortality and follow-up events were not significantly increased in patients with ACS and concomitant chronic kidney disease (eGFR < 60 mL/kg/m2) for whom an early invasive approach was preferred (18). Patel et al. (19) had also found that the incidence of acute kidney injury requiring dialysis and in-hospital mortality among patients with chronic kidney disease and ACS were not significantly related to the timing of PCI. Recent studies showed that 7 - 36% of patients with COVID-19 infection develop myocardial injury (20,21). The results of a meta-analysis by Santoso A. et al. (22) demostrated that acute myocardial injury concomitant with COVID-19 infection was associated with a more severe clinical picture (RR 13.81, $p < 0.001$; I2: 0%), more frequent hospitalizations in intensive care units (RR 7.94, $p = 0.01$; I2: 79%), and higher mortality rates (RR 7.95, $p < 0.001$; I2: 65%). The results of an observational cohort study also revealed that patients with COVID-19 and ACS had higher in-hospital (OR: 3.27; 95% (CI): 2.41 - 4.42) and thirty-day (OR: 6.53, 95% CI: 5.1 - 8.36) mortality, compared to patients with ACS without a diagnosis of COVID-19 infection (23). The SARS-CoV-2 virus can directly cause myocardial injury by entering cardiomyocytes through the angiotensin-converting enzyme 2 (ACE-2) receptors. Upon binding to the ACE-2 receptors, the virus leads to the downregulation of these receptors, resulting in decreased synthesis of angiotensin (1-7) and increased activity of angiotensin II. The predominance of angiotensin II then triggers a cascade of pathological processes, including systemic vasoconstriction, apoptosis, inflammation, and proliferation, ultimately leading to de novo cardiomyocyte damage or worsening of pre-existing cardiovascular disease. In addition to the direct viral effects, COVID-19-associated myocardial injury can also be mediated by indirect mechanisms, such as cytokine release, microvascular dysfunction (due to intravascular coagulation and thrombosis), hypoxemia, and inflammation. These factors can contribute to myocardial injury by destabilizing existing atherosclerotic plaques and causing an increase in cardiac troponin levels (21,24). We found in our study that COVID-19 infection was an independent predictor of in-hospital mortality in patients with ACS (OR: 2.01, 95% CI [1.425 - 4.615], $p = 0.012$).

Limitations of the study

First of all, this study was a retrospective, single-center study with a relatively small sample size, which limits the ability to make definitive conclusions about the underlying pathophysiological mechanisms and generalizability. Another limitation of our study is that the decision for intervention was based on the operator's clinical experience rather than fractional flow reserve measurements.

Conclusion

We found that advanced age, low serum albumin, elevated bilirubin, BUN, cardiac troponin levels, and COVID-19 infection were linked to increased in-hospital mortality in patients with acute coronary syndrome referred from other clinics. Notably, percutaneous intervention was associated with a reduction in in-hospital mortality for this patient population.

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Conflict of interest statement

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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