ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Clinical implications and indicators of mortality among patients hospitalized with concurrent COVID-19 and myocardial infarction

COVID-19 ve miyokart enfarktüsü ile hastaneye yatan hastalarda klinik implikasyonlar ve mortalite göstergeleri

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ABSTRACT

Objective: Acute ischemic cardiac events can complicate coronavirus disease 2019 (COVID-19). This study aimed to report in-hospital characteristics of patients with acute myocardial infarction and concomitant COVID-19.

Methods: This was a registry-based retrospective analysis of patients admitted with positive COVID-19 tests who suffered from acute myocardial infarction either before or during hospitalization. This study was conducted from March 01 to April 01, 2020, in a tertiary cardiovascular center, the Tehran Heart Center. We performed an exploratory analysis to compare the clinical characteristics of patients who died during hospitalization or were discharged alive.

Results: In March 2020, 57 patients who had acute myocardial infarction and a confirmed diagnosis of COVID-19 were included in the study. During hospitalization, 13 patients (22.8%) died after a mean hospital stay of 8.4 days. The deceased were older than the survivors. No significant association between mortality and sex or length of hospital stay was observed. Individuals with hypertension were more likely to have a fatal outcome. Previously receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers did not show any association with mortality. Regarding the laboratory data during hospitalization, higher cardiac troponin T, neutrophil count, C-reactive protein, urea, and blood urea nitrogen/creatinine ratio were observed in the mortality group. The deceased had a lower lymphocyte count than the survivors.

Conclusion: Markers of worsening renal function and immune system disturbance seem to be associated with mortality in concurrent acute myocardial infarction and COVID-19. Optimizing the management of acute coronary syndrome complicating COVID-19 requires addressing such potential contributors to mortality.

ÖZET

Amaç: Akut iskemik kardiyak olaylar 2019 koronavirüs hastalığını (COVID-19) komplike hale getirebilir. Bu çalışma, akut miyokart enfarktüsü ve beraberinde COVID-19 hastalığı olan hastaların hastane içi özelliklerini raporlamayı amaçlamıştır.

Yöntem: Bu çalışma, hastaneye yatmadan önce veya yatış sırasında akut miyokart enfarktüsü geçiren ve COVID-19 testi pozitif olarak hastaneye kabul edilen hastaların kayıt tabanlı retrospektif bir analizidir. Çalışma, 01 Mart-01 Nisan 2020 tarihleri arasında Tahran Kalp Merkezi'nde gerçekleştirilmiştir. Hastanede hayatını kaybeden veya taburcu olan hastaların klinik özelliklerini karşılaştırmak için keşifsel analiz yapılmıştır.

Bulgular: Mart 2020'de, akut miyokart enfarktüsü geçiren ve COVID-19 tanısı konan 57 hasta çalışmaya dahil edildi. Hastanede kalış süresinde, ortalama 8.4 gün içerisinde toplam 13 hasta (%22.8) öldü. Ölen hastalar hayatta kalanlardan daha yaşlıydı. Mortalite ile cinsiyet veya hastanede kalış süresi arasında anlamlı bir ilişki gözlenmedi. Hipertansiyonu olan bireylerin ölüm oranı daha yüksekti. Daha önce anjiyotensin dönüştürücü enzim inhibitörleri veya anjiyotensin II reseptör blokerleri alınması ile mortalite arasında bir ilişki görülmedi. Hastanede yatış sırasındaki laboratuvar verilerine bakıldığında, mortalite grubunda daha yüksek kardiyak troponin T, nötrofil sayısı, C-reaktif protein, üre ve kan üre nitrojen/kreatinin oranı gözlendi. Ölen hastalarda lenfosit sayısı, hayatta kalanlardan daha düşüktü.

Sonuç: Eş zamanlı gelişen akut miyokart enfarktüsü ve COVID-19'da mortalite böbrek işlevlerinin kötüleşmesi ve bağışıklık sistemi bozukluğuyla ilişkili görünmektedir. COVID-19'u komplike hale getiren akut koroner sendromun yönetiminin optimize edilmesi için mortalite oranına etkisi olan bu tür olası faktörleri göz önünde tutmak gerekmektedir.

Received: July 31, 2020 *Accepted:* January 31, 2021
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Patients with underlying cardiovascular disease are more likely to develop severe forms of coronavirus disease 2019 (COVID-19).[1] Importantly, the infection itself can precipitate cardiovascular complications.[1,2] Mononuclear myocardial infiltration, myocardial injury, and myocarditis have been documented with COVID-19.[2-4] Moreover, through overt inflammation, plaque destabilization, coagulation disturbances, and alterations in myocardial supply and demand, COVID-19 infection can result in ischemia and acute myocardial infarction (AMI).[2,4,5]

As the number of COVID-19 cases increases, identifying complications and prognostic factors becomes crucial, especially in cardiovascular comorbidities associated with severe infection.[2] Despite the potentially higher incidence of AMI with COVID-19 during this pandemic and a number of published studies describing patients with COVID-19 and AMI[6-8] many of the diagnostic, prognostic, and therapeutic aspects of this clinical entity remain unknown. Therefore, this study aimed to describe the in-hospital characteristics of a patient population admitted with AMI and concurrent COVID-19.

METHODS

Study design

This study was conducted on the basis of a registry of COVID-19 from a single tertiary cardiovascular center, the Tehran Heart Center (THC). The data are reported as a case series of patients with concomitant AMI and COVID-19. This study complied with the ethical principles of the declaration of Helsinki and was supervised by the research ethics committee of Tehran University of Medical Sciences (approval ID: IR.TUMS.VCR.REC.1399.011).

Patient population and data collection

After the announcement of the COVID-19 outbreak in Iran on February 19, 2020, suspected patients have been tested and followed in an integrated registry at THC. Inclusion in the study required confirmation of COVID-19 with diagnostic tests performed at the time of admission and AMI presenting either before or during hospitalization. The COVID-19 diagnostic work-up was performed according to the Iranian ministry of health (available from https://irimc.org/) and the World Health Organization recommendations,[9] which utilize computed tomography scanning and reverse transcription-polymerase chain reaction tests. The definition of AMI was based on the fourth universal definition.[10]

Patient data, including demographics, clinical presentation, diagnostic tests, medical history, treatments, and clinical course, were recorded by trained staff during hospitalization. Hypertension, diabetes mellitus, and dyslipidemia were defined according to previously documented diagnosis with the initiation of risk-factor-directed management. History of coronary artery disease and heart failure with reduced ejection fraction was based on previous symptoms and documented diagnostic testing. Complete blood count and differential, C-reactive protein (CRP), urea, and creatinine (Cr) were checked daily. The laboratory results of the day of admission and the last day before discharge or death were entered into the database. High-sensitive cardiac troponin T (hs-cTnT) was recorded at 0 and 3 hours for all the patients.

Abbreviations:

ACEi	*Angiotensin-converting enzyme inhibitors*
AMI	*Acute myocardial infarction*
ARB	*Angiotensin II receptor blockers*
BUN	*Blood urea nitrogen*
CABG	*Coronary artery bypass grafting*
CAG	*Coronary angiography*
COVID-19	*Coronavirus disease 2019*
Cr	*Creatinine*
CRP	*C-reactive protein*
hs-cTnT	*High-sensitive cardiac troponin T*
NSTEMI	*Non-ST elevation myocardial infarction*
STEMI	*ST-elevation myocardial infarction*
THC	*Tehran Heart Center*
TIMI	*Thrombolysis in myocardial infarction*

Mortality

All-cause in-hospital mortality was assessed in the study. We aimed to compare the clinical features between those who died during hospitalization and those who were discharged alive. Such exploratory analysis was performed to identify potential factors associated with mortality. The decision for discharge required improvement in clinical symptoms, cessation of fever without a need for antipyretics, and no need for invasive ventilation.

Statistical analysis

Categorical variables were reported as numbers (percentages). Continuous variables were reported as mean±standard deviation or median (interquartile range) if there was a skewed distribution. In an exploratory analysis, we compared patients with and without a fatal outcome during hospitalization. To compare categorical variables, in cases of 2×2 contingency tables, we used

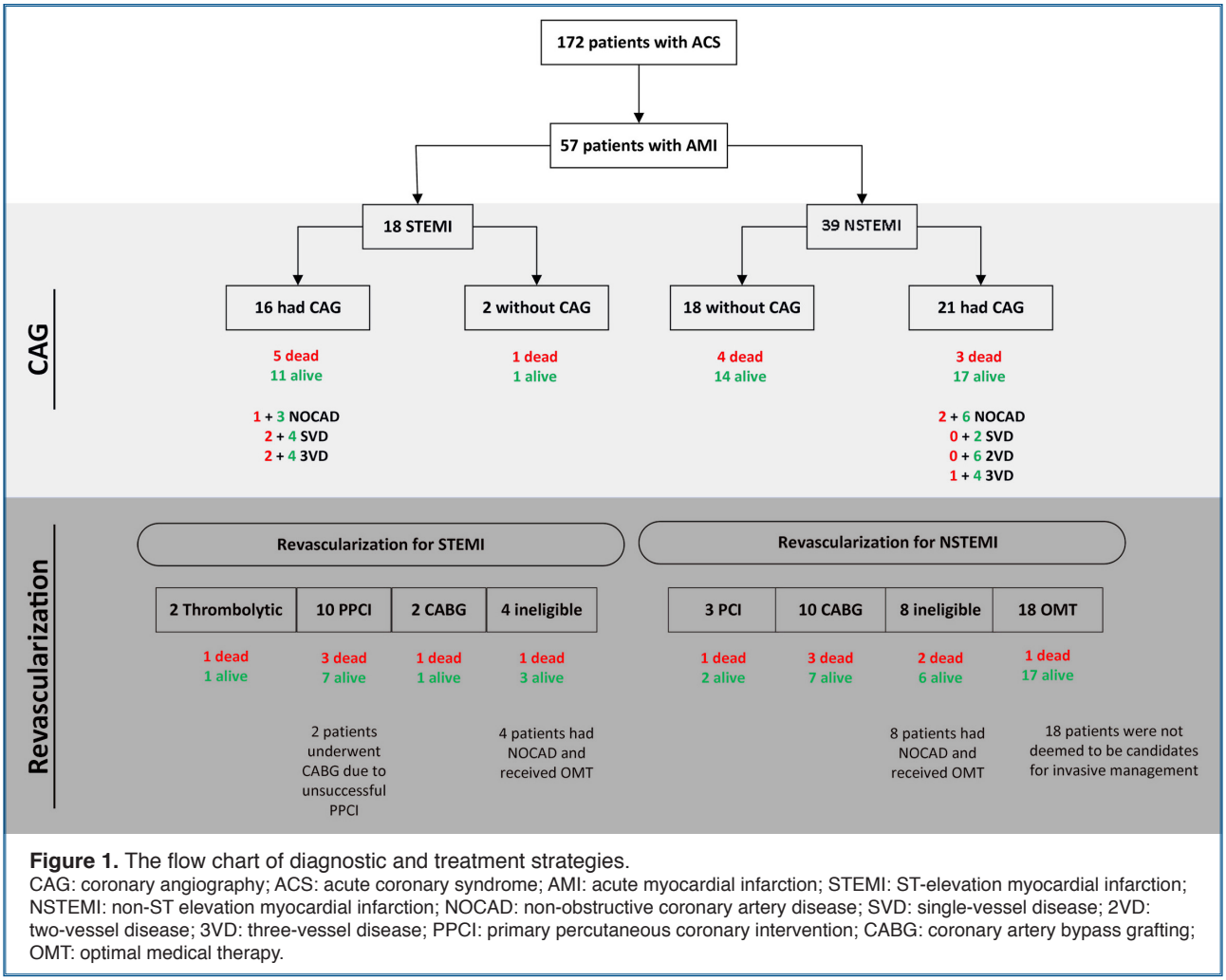

Figure 1. The flow chart of diagnostic and treatment strategies.
CAG: coronary angiography; ACS: acute coronary syndrome; AMI: acute myocardial infarction; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; NOCAD: non-obstructive coronary artery disease; SVD: single-vessel disease; 2VD: two-vessel disease; 3VD: three-vessel disease; PPCI: primary percutaneous coronary intervention; CABG: coronary artery bypass grafting; OMT: optimal medical therapy.

chi-squared test with the Yates continuity correction in cases where one or more of the cells had an expected frequency of 5-25. When the expected frequency of 1 or more cells was 5 or less, we used Fisher's exact test. In R×C contingency tables, we used the Fisher-Freeman-Halton test in patients where at least 1 cell had an expected frequency of ≤ 5. For continuous variables, the assumption of normal distribution was assessed by the Kolmogorov-Smirnov normality test, along with the visual examination of the histograms, Q-Q plots, and the values and standard errors of kurtosis and skewness. In case of acceptance of the normality assumption, student *t*-test was performed; otherwise, the non-parametrical Mann-Whitney U test was used to compare variables. We used repeated measures analysis of variance to assess the differences in laboratory results. To make the assumption of normality, we performed Box-Cox transformation on the laboratory variables before the repeated-measures analysis of variance. The level of statistical significance was set at <0.05. All analyses were performed using the SPSS software for Windows, version 23.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

Data collection was performed from March 01 to April 01, 2020. Overall, 264 patients were admitted to THC during this period, among whom 172 presented with acute coronary syndromes. After applying eligibility criteria, 57 patients with concurrent AMI and confirmed COVID-19 were included in the analysis. Around one-third of the study population had ST-elevation (i.e., ST-elevation myocardial infarction [STEMI]) on admission electrocardiogram. A flow chart of diagnostic and therapeutic approaches in the study population is demonstrated in Figure 1. The most common symptoms attributable to COVID-19 were dyspnea (63.2%), fever (26.3%), and cough (22.8%).

Table 1. Demographic and clinical features

	Outcome of hospitalization			
	Total (n=57)	Deceased (n=13)	Alive (n=44)	*p*
Age, years	65.6±12.5	70±14.4	64.3±11.7	0.151
Sex (male)	38 (66.7%)	9 (69.2%)	29 (65.9%)	>0.999
Duration of hospitalization, d*	7.0 (4.0-11.5)	6.0 (3.0-13.0)	7.0 (5.0-11.0)	0.593
STEMI	18 (31.6%)	6 (46.2%)	12 (27.3%)	0.308
NSTEMI	39 (68.4%)	7 (53.8%)	32 (72.7%)	
Coronary angiogram	37 (64.9%)	8 (61.5%)	29 (65.9%)	>0.999
Non-obstructive disease	12 of 37 (32.4%)	3 of 8 (37.5%)	9 of 29 (31%)	0.651
Single-vessel disease	8 of 37 (21.6%)	2 of 8 (25%)	6 of 29 (20.7%)	
Two-vessel disease	6 of 37 (16.2%)	0 of 8 (0%)	6 of 29 (20.7%)	
Three-vessel disease	11 of 37 (29.7%)	3 of 8 (37.5%)	8 of 29 (27.6%)	
Revascularization				
PPCI	10 (17.5%)	3 (23.1%)	7 (15.9%)	0.680
CABG	14 (24.6%)	4 (30.8%)	10 (22.7%)	0.715
Ejection fraction, %*	40.0 (30.0-50.0)	35.0 (25.0-40.0)	42.5 (33.5-50.0)	0.063
Presentation, vital signs				
Temperature, °C*	36.8 (36.5-37.2)	36.8 (36.5-37.1)	36.9 (36.5-37.2)	0.811
Respiratory rate, min*	18.0 (18.0-19.8)	18.0 (17.0-19.5)	18.0 (18.0-20.0)	0.776
Pulse rate, min*	79.0 (70.5-96.5)	96.0 (71.5-117.0)	78.0 (70.3-93.3)	0.168
Systolic blood pressure, mmHg	129.9±25.7	132.0±23.5	129.2±26.5	0.736
Diastolic blood pressure, mmHg	79.0±16.8	82.1±20.5	78.1±15.7	0.453
Oxygen saturation, %*	95.0 (92.0-96.0)	95.0 (87.0-97.5)	94.0 (92.0-95.8)	0.546
Cardiovascular risk				
Hypertension	37 (64.9%)	10 (76.9%)	27 (61.4%)	0.346
Diabetes mellitus	32 (56.1%)	6 (46.2%)	26 (59.1%)	0.612
Insulin use	8 of 32 (25.0%)	3 of 6 (50.0%)	5 of 26 (19.2%)	0.148
Dyslipidemia	25 (43.9%)	4 (30.8%)	21 (47.7%)	0.445
Current smoking	19 (33.3%)	3 (23.1%)	16 (36.4%)	0.510
History of CAD	35 (61.4%)	8 (61.5%)	27 (61.4%)	>0.999
History of HFrEF	7 (12.3%)	2 (15.4%)	5 (11.4%)	0.653
Drug history				
Statin	35 (61.4%)	9 (69.2%)	26 (59.1%)	0.737
ACEi or ARB	37 (64.9%)	8 (61.5%)	29 (65.9%)	0.754

d: day; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; PPCI: primary percutaneous coronary intervention; CABG: coronary artery bypass grafting; CAD: coronary artery disease; HFrEF: heart failure with reduced ejection fraction; ACEi: angiotensin-converting-enzyme inhibitors; ARB: angiotensin II receptor blocker; min: minimum.
Data are reported as mean±standard deviation, median (interquartile range), or number (%).
*p is reported according to the Mann-Whitney U test.

A total of 37 patients underwent coronary angiography (CAG) during their hospitalization, of whom 12 patients did not have any evidence of obstructive disease (Table 1). During the COVID-19 pandemic, the quality of care for patients with AMI has decreased with alterations in access to care and treatment strategies.[11] In this registry, 2 patients with ST-elevation had received thrombolytic therapy at

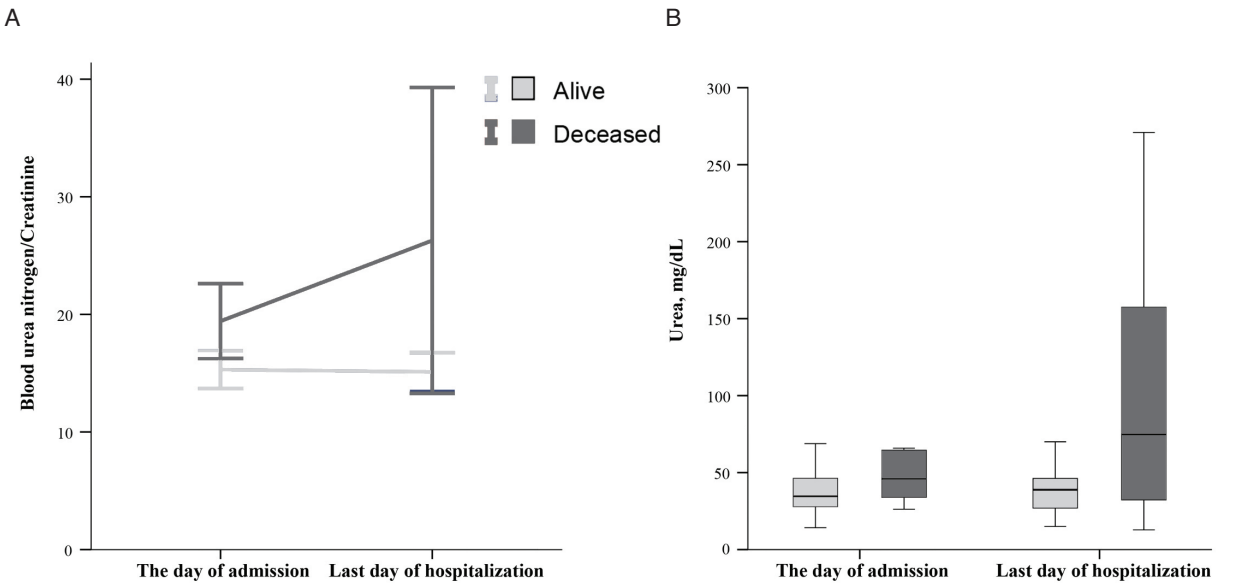

Figure 2. Markers of kidney function. **(A)** Blood urea nitrogen to creatinine ratio depicted by mean and error bars for 95% confidence intervals. **(B)** Boxplot for urea during hospitalization.

another center and had resolution of ischemia at the time of admission. Among patients without ST-elevation (i.e., patients with non-ST elevation myocardial infarction [NSTEMI]), CAG was delayed in 6 patients because of late presentation and critical illness—2 patients with acute kidney injury and 4 with severe acute respiratory distress requiring intubation. Furthermore, 12 patients with NSTEMI were deemed stable and low-risk by the treating physician and received medical management. The revascularization strategy during the study period was heterogeneous. Of the patients with STEMI, 2 received thrombolytics, 10 underwent primary percutaneous coronary intervention (2 of these primary percutaneous coronary intervention procedures were unsuccessful and followed by coronary artery bypass grafting [CABG]), 2 were directly referred for CABG after evaluation of their coronary anatomy, and 4 had non-obstructive coronary artery disease. Moreover, 3 patients with NSTEMI had percutaneous management and 10 had CABG, whereas 8 patients had non-obstructive coronary disease with no revascularization, and 18 lesions were managed medically.

In-hospital mortality occurred in 13 patients (22.8%) after a mean hospital stay of 8.4 days. During hospitalization, 19 patients (33.4%) were eventually intubated, among whom 11 (57.9%) passed away.

Population characteristics

The clinical data at the time of presentation are summarized in Table 1. The patients who died were older than the survivors, although age was not significantly associated with mortality. No meaningful association was observed between length of hospital stay and mortality. The oxygen saturation at presentation and ejection fraction were numerically lower among those who died. Conventional cardiovascular risk factors did not significantly correlate with mortality, although patients with hypertension and patients with diabetes who toon insulin injectionswere more likely to have a fatal outcome. Importantly, previously receiving angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) did not show any association with mortality.

Among patients who had CAG, 6 had evidence of left main disease. Moreover, 10 patients had total occlusion of the vessel and 2 had evidence of chronic total occlusion. Of the 37 patients who had CAG, 12 (3 deceased; 9 alive) had no obstructive lesions in their coronaries. Of the 13 patients who underwent percutaneous coronary intervention, 8 had a baseline thrombolysis in myocardial infarction (TIMI) flow grade of 0 or 1. After the procedure, a TIMI flow grade of 3 was only achieved in 6 patients. There was no evidence of no-reflow phenomenon detected

Table 2. Laboratory results

	Outcome of hospitalization				*p*
	Total (n=57)	Deceased (n=13)	Alive (n=44)	Time × Survival	Between subjects
Laboratory results at presentation					
White blood cells, μL	9300 (7150-12500)	9300 (7650-12600)	9200 (6725-12285)		See below
Lymphocyte count, μL	1836 (1277-2382)	1989 (1349-2858)	1803 (1262-2355)		See below
Neutrophil count, μL	6009 (4399-9846)	6556 (5809-10120)	5871 (4230-9405)		See below
Hemoglobin, g/dL	14.0 (12.1-15.4)	14.0 (12.1-15.2)	14.1 (12-15.5)		See below
Platelets, 103/μL	201 (164-272)	232 (200-275)	196 (150-270)		See below
Mean platelet volume, fL	10.0 (9.3-10.8)	9.8 (9.3-10.5)	10.0 (9.3-11.3)		See below
CRP, mg/L	4 (0.8-12.6)	5.1 (2.1-18.3)	3.7 (0.7-11.6)		See below
Urea, mg/dL	36.7 (28.5-50.8)	46 (32.6-96)	34.6 (27.4-46.4)		See below
Creatinine, mg/dL	1.2 (1.0-1.7)	1.4 (1.1-2.4)	1.2 (1.0-1.7)		See below
BUN/Creatinine	15.7 (12.5-19.7)	20.2 (13.1-23.3)	14.9 (12.4-16.9)		See below
Hs-cTnT 0-hr, ng/L	212 (49-1268)	1475 (222-6657)	128 (38-518)	0.681	0.007
Hs-cTnT 3-hrs, ng/L	561 (169-4779)	3237 (724-9764)	313 (87-1413)		
Laboratory results on final day of hospitalization					
White blood cells, μL	8400 (6900-11585)	12210 (8800-19810)	7900 (6200-9900)	0.055	0.009
Lymphocyte count, /μL	1852 (1221-2709)	1037 (649-1548)	2116 (1434-2844)	0.001	0.043
Neutrophil count, /μL	5614 (4053-8421)	10085 (7031-12902)	4782 (3762-6543)	0.022	0.002
Hemoglobin, g/dL	11.9 (10.4-13.7)	9.4 (8.8-12.1)	12.0 (10.8-14.0)	0.008	0.107
Platelets, 103/μL	230 (159-310)	216 (150-274)	237 (159-314)	0.057	0.502
Mean platelet volume, fL	10.0 (9.0-10.6)	10.0 (8.9-10.4)	10.0 (9.0-10.6)	0.341	0.643
CRP, mg/L	4.1 (1.4-9.2)	19.5 (8.7-31.2)	3 (0.9-5.4)	0.293	< 0.001
Urea, mg/dL	40.1 (27.0-51.0)	74.8 (26.7-164.1)	38.8 (27-46.3)	0.884	0.012
Creatinine, mg/dL	1.3 (1.0-1.9)	1.9 (1.1-4.5)	1.2 (0.9-1.7)	0.050	0.196
BUN/Creatinine	15.2 (12.0-20.8)	23.8 (10.6-37.6)	14.9 (12.0-18.3)	0.684	0.007

CRP: C-reactive protein; hs-cTnT: high-sensitive cardiac troponin T; BUN: blood urea nitrogen.
Data are reported as median (25th percentile-75th percentile) or number (%). Analysis of laboratory data was conducted with repeated measures analysis of variance.

on CAG. As mentioned earlier, 2 patients had failed intervention without restoration of flow and were referred for CABG because of their coronary anatomy.

After AMI, 3 patients had sustained ventricular tachycardia, which required electrical cardioversion, and none of them were lethal. One patient was admitted with severe pericardial effusion, for whom pericardial drainage was performed. The patient did not have any evidence of myocardial wall rupture and was discharged after recovery. Among patients without a prior history of heart failure with reduced ejection fraction, 13 had an ejection fraction of less than 40% after AMI. Furthermore, 2 patients had cardiogenic shock during hospitalization.

Laboratory data

The laboratory data are summarized in Table 2. At the time of admission, the deceased showed higher hs-cTnT levels from 0 to 3 hours compared to the survivors (between subjects p=0.700). The number of white blood cells was higher among the deceased (between subjects p=0.009), but there was no interaction between the 2 groups. Although neutrophil count trended higher in the group who died (p for interaction=0.022), lymphocyte count (p for interaction=0.001), and hemoglobin levels (p for interaction=0.008) trended downwards. The level of CRP, urea, and blood urea nitrogen (BUN) to Cr ratio were higher in the mortality group (between sub-

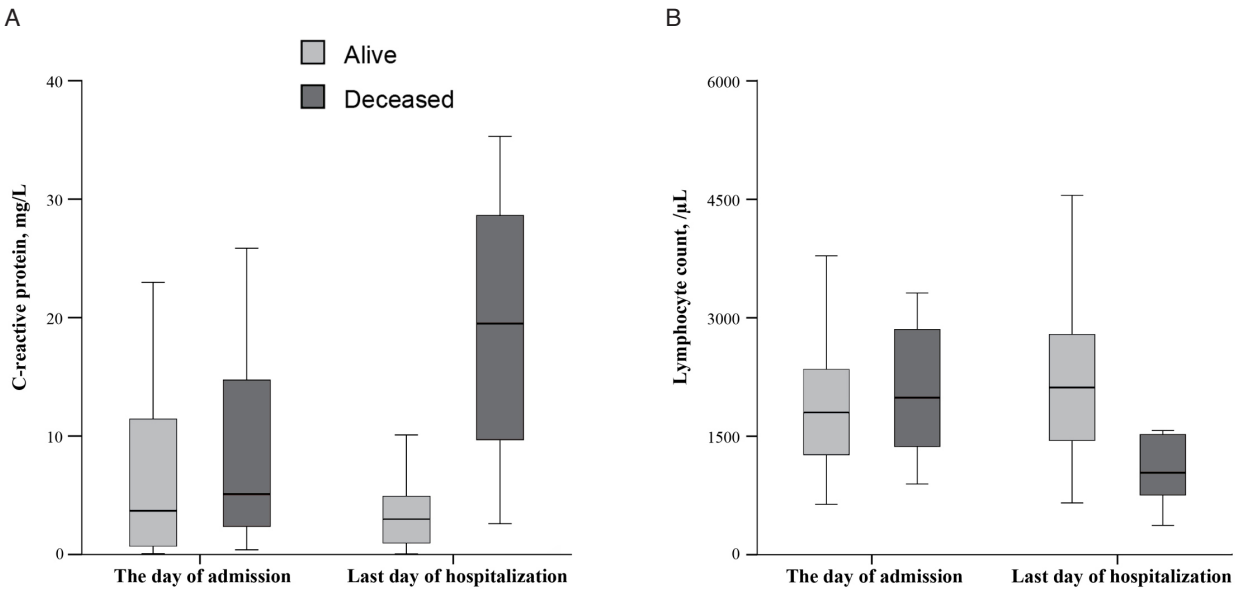

Figure 3. Markers of immune system. Boxplots for **(A)** C-reactive protein and **(B)** lymphocyte count during hospitalization.

jects p<0.001, p=0.120, and p=0.007, respectively); however, there was no interaction detected for any of these 3 (Figures 2 and 3).

DISCUSSION

Mortality

As of April 16, 2020, the case-fatality rate of COVID-19 is reported around 6.1% worldwide and 6.3% in Iran.[12] On the other hand, a previous analysis from the THC reported the overall in-hospital mortality rate of 1.26% among all the patients who had a diagnosis of acute coronary syndrome.[13] Against this background, the mortality rate among our participants was 22.8%, which gives a hint on how deadly the combination of COVID-19 infection and AMI can be. The association of cardiovascular comorbidities with mortality in COVID-19 has been reported from China and Italy;[1,14] however, concurrent AMI and COVID-19 has not been studied extensively. As hypoxia was a prominent feature among those who died, most of whom were eventually intubated, rapid progression of COVID-19 could be considered as the underlying cause of such high mortality. Whether the incidence of AMI itself was precipitated by the acute viral infection remains uncertain. Furthermore, higher mortality among patients with AMI and COVID-19 could be due to a longer delay between symptom onset and access to proper care.[11,15]

According to annual reports at THC, the number of hospitalized patients with acute coronary syndromes was 401 in March 2019 compared with 172 in March 2020. Similarly, hospitals in other epicenters of the pandemic have reported declines in the number of AMI presentations.[16,17] This trend sounds alarming as there is every reason for an increase in the incidence of AMI during a viral pandemic and not the opposite,[4,16] which could mean a certain number of patients with AMI are not receiving appropriate cardiovascular care. Moreover, the number of patients who received CAG was way lower than standard practice in this study, which was conducted during the early days of the COVID-19 pandemic. This underlies a lower quality of care, which can contribute to higher mortality rates among patients with COVID-19 and AMI.

Cardiovascular disease and risk factors

As expected, mortality was associated with numerically higher STEMI cases, hs-cTnT levels, and lower ejection fraction. Most patients hospitalized for COVID-19 have comorbid conditions, which most probably have a causal association with disease severity.[4] The mortality risk with COVID-19 is higher in all age groups in the presence of such comorbid-

ities, most notably hypertension, obesity, diabetes, and coronary artery disease.[18] According to our results, in a population with concomitant COVID and AMI, the number of patients with hypertension and patients with diabetes who injected insulin was noticeably higher among the deceased, although none showed statistical significance owing to the limited sample size. Our finding that consumption of ACEi/ARBs was not different between the 2 groups is in accordance with previous studies.[19]

The number of current smokers was non-significantly higher in deceased patients. The current evidence for the relationship between COVID-19 and smoking is inconclusive. A recent systematic review concluded that smoking is associated with worse outcomes of COVID-19.[20] However, a meta-analysis of current data by Lippi and Henry[21] have shown no association between active smoking and severe disease. Nonetheless, previous observations from the Middle East Respiratory Syndrome epidemic, the inflammatory processes initiated by smoking in the respiratory system, and the upregulation of viral entry receptors in smokers, suggest a worse prognosis with smoking.[22]

Notably, about one third of patients who underwent CAG had no obstruction in coronary arteries. This finding is in accordance with previous reports where up to 40% of patients with COVID-19 and STEMI had no evidence of a culprit lesion.[6] Such a clinical picture can be explained by the presence of type 2 AMI, or even non-AMI myocardial injury. Currently, there is no consensus on how to reliably differentiate between these entities in patients with COVID-19 as AMI can be the first presentation in such patients.[6]

Renal function

An important observation was that urea, Cr, and the BUN to Cr ratio were considerably higher in patients who died. This difference was expanded over the course of hospitalization, meaning that the renal function worsened among the deceased (Figure 2). The probable mechanistic pathways of worsening renal function in the setting of COVID-19 and AMI are interconnected and require further investigation.[23]

Increased cytokine release associated with COVID-19[24,25] can result in renal inflammation, systemic endothelial injury, and increased vascular permeability, which in turn may lead to intravascular volume depletion, decreased glomerular filtration, and renal hypoperfusion.[23] Along with the dehydration associated with fever and hyperventilation, reduced intravascular volume can occur because of reduced cardiac output in the setting of AMI, which can result in the development of cardiorenal syndrome type 1.[23] On the basis of the BUN/Cr ratio, it can be suggested that in our study population, dehydration and pre-renal acute kidney injury played a significant role in renal deterioration. It is worth noting that in the setting of AMI, the capability to replace fluids can be limited by the reduced cardiac function. Furthermore, there has been evidence of an association between alveolar inflammation in acute respiratory distress syndrome and kidney tubular damage, the so-called lung-kidney axis.[26] COVID-19 infection can cause profound hypoxia in severe cases,[24] which might as well translate into renal medullary hypoxia and worsened renal function.

Immune system

A rise of CRP level, along with neutrophilia and lymphopenia, were associated with a fatal outcome; however, the survivors demonstrated improvements in these markers of inflammation. This observation is consistent with the current evidence proposing that a rise in CRP and lymphopenia indicate poor prognosis in COVID-19.[27] Recent data on the pathogenesis of COVID-19 has highlighted the central role of immune overactivation, followed by the development of cytokine storm leading to tissue injury.[28] The growing evidence emphasizing the role of the immune system in cardiovascular events has led to the investigation of immune-modifying agents in the management of AMI.[29] Based on this concept, further research is warranted to clarify this issue, which might enable cardiologists to use immune modification as a novel therapeutic approach during the COVID-19 pandemic for the management of cardiovascular events in the setting of COVID-19 infection.

Limitations

This study was a retrospective analysis with a limited sample size. The current sample appears to have insufficient power to determine the factors associated with mortality, hence larger populations should be studied through longer follow-ups to draw firm conclusions. This study could have been improved by including a control group of patients presenting with AMI without

COVID-19 infection to compare the characteristics associated with COVID-19 in such setting. Because of the lack of a control group, none of the study findings should be extrapolated to compare, in any way, patients with COVID-19 to those without. The number of CAGs and reperfusion strategies are different in everyday practice and should be noted when interpreting the findings. As mentioned before, one contributor to the high mortality in the study could be the longer time from symptom onset to presentation in patients with AMI during the pandemic. A comparison of such time-interval between patients with AMI and with and without COVID-19 could clarify this issue. Moreover, because of the restricted conditions at COVID-19 isolation wards, other clinically relevant data regarding the cardiovascular system and COVID-19 pathophysiology were not available in this study. This study was a case series with exploratory analyses; hence, we advise caution in interpreting the findings. Finally, it should be noted that this data is preliminary, and future research is necessary to evaluate the characteristics of this condition.

Conclusion

Among the 57 patients hospitalized with AMI and tested positive for COVID-19, after a mean of 8.4 days of hospitalization, 22.8% died. Worsening renal function and immune system disturbance seemed to be associated with mortality. Although our findings are not conclusive, they underline the high risk for mortality in this patient group and the need for more data to optimize AMI management during the COVID-19 pandemic.

Ethics Committee Approval: Ethics committee approval was received for this study from the Research Ethics Committee of Tehran University of Medical Sciences (Approval Date: March 21, 2020; Approval Number: IR.TUMS.VCR.REC.1399.011).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - M.T., S.S., H.P.; Design - H.T., K.H., M.T.; Supervision - K.H., M.T.; Materials - H.T., M.M., B.S., F.M., B.S., A.S., M.P., A.A.; Data - F.M., B.S., M.P., A.A., M.L.T.; Analysis - H.T., K.H., M.P., A.A., M.M.; Literature search - H.T., M.M., R.M.B; Writing - H.T., M.M., M.T., K.H.; Critical revision - M.T., H.T, K.H., S.S., H.P., M.L.T., F.M., B.S., M.M., A.S., R.M.B., M.P., A.A.

Funding: No funding was received for this research.

Conflict-of-interest: None.

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Keywords: Myocardial infarction; acute coronary syndrome; COVID-19

Anahtar Kelimeler: Miyokart enfarktüsü; akut koroner sendrom; COVID-19