

THE PREDICTORS OF MORTALITY IN PATIENTS WHO WERE REFERRED TO CORONARY ANGIOGRAPHY DUE TO MYOCARDIAL INFARCTION AND HAD COVID-19

MİYOKARD ENFARKTÜSÜ NEDENLİ KORONER ANJİYOGRAFİYE YÖNLENDİRİLEN COVID-19 HASTALARINDA MORTALİTE PREDİKTÖRLERİ

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ABSTRACT

Introduction: The mortality and morbidity data are limited because the patients who presented with myocardial infarction and had COVID-19 were not followed for an extended period. This study aimed to investigate mortality predictors in this group.

Method: Eighty patients with COVID-19 infection who performed invasive coronary angiography due to high-risk myocardial infarction were enrolled. All patients were followed at least one year after the first admission. Mortality data and medical records were retrospectively collected using the hospital's medical record software.

Results: Thirty-four patients (42.5%) died one year after the first admission. Thirty of them (88.2%) were in-hospital mortality. The median door-to-procedure time was 107.5 minutes (17-1278). PCI was performed in 49 patients (61.25%). Higher ferritin and LDH were independent factors related to mortality (OR: 1.006, CI 95%: 1.001-1.01, p: 0.011; OR:1.005, CI 95%: 1.001-1.009, p:0.025; respectively). The cut-off value was estimated at 211 mcg/L for ferritin (AUC:0.762, sensitivity: 73.5%, specificity 63%, p:<0.001) and 492 U/L for LDH (AUC:0.863, sensitivity: 79.4%, specificity 80.4%, p:<0.001).

Conclusion: Despite invasive management, the mortality rate in patients with myocardial infarction and COVID-19 is high. Only increased LDH and ferritin levels were independent predictors of mortality.

Keywords: Myocardial Infarction, COVID-19, Coronary Angiography, Mortality

ÖZET

Giriş: Miyokard enfarktüsü tablosu ile başvuran COVID-19 hastalarında mortalite ve morbidite verileri hastaların uzun süreli takiplerinin olmaması nedeniyle kısıtlıdır. Bu çalışmada bu hasta grubunun mortalite prediktörlerinin araştırılması amaçlanmıştır.

Yöntemler: COVID-19 enfeksiyonu mevcut olan ve yüksek riskli miyokard enfarktüsü nedeniyle invaziv koroner anjiyografi yapılan 80 hasta çalışmaya dahil edilmiştir. Tüm hastalar ilk başvurudan sonra en az 1 yıl süre ile takip edilmiştir. Hastaların mortalite verileri ve medikal kayıtları hastanenin medikal kayıt programından retrospektif olarak alınmıştır.

Bulgular: Otuz dört hastanın (%42,5) ilk başvurudan sonraki bir yıllık takipte öldüğü izlendi. Bu hastaların 30'u (%88,2) ilk başvurudaki hastane yatışı sonlanmadan öldü. Medyan kapı balon süresi 107,5 dk (17-1278) olarak izlendi. 49 hastaya (%61,25) invaziv koroner anjiyografi sırasında perkütan koroner girişim uygulandı. Yüksek ferritin ve LDH seviyelerinin mortalite ile bağımsız olarak ilişkili olduğu izlendi (OR: 1,006, CI %95: 1,001-1,01, p: 0,011; OR:1,005, CI %95: 1,001-1,009, p:0,025; sırasıyla). Ferritin için kestirim değeri 211 mcg/L (AUC:0.762, sensitivite: 73.5%, spesifite 63%, p:<0.001) ve LDH için kestirim değeri 492 U/L (AUC:0.863, sensitivite: 79.4%, spesifite 80.4%, p:<0.001) olarak hesaplandı.

Sonuç: İnvaziv medikal tedaviye rağmen miyokard enfarktüsü gelişen COVID-19 hastalarında mortalite oranı yüksektir. Çalışmada artmış LDH ve ferritin seviyelerinin mortalite prediktörü olduğu izlenmiştir.

Anahtar Kelimeler: Miyokard Enfarktüsü, COVID-19, Koroner Anjiyografi, Mortalite

INTRODUCTION

The coronavirus 2019 (COVID-19) pandemic is among the most critical health problems worldwide. Because the multisystemic involvement of COVID-19 infection affects the nature of the disease as it affects social life (1, 2). Acute respiratory distress syndrome is a leading problem in intensive care units for patients with COVID-19 (3). In addition, the tendency to thromboembolic events can cause pulmonary embolism, thrombosis of deep veins, ischemic stroke, and myocardial infarction in the covid infection (4, 5). Also, some hypotheses assert that acute respiratory

distress syndrome and coagulopathies in covid infection could share the exact pathophysiology: cytokine storm (6).

Acute myocardial infarction and cardiovascular diseases are the most common reason for mortality in many countries (7). Many prognostic factors for acute myocardial infarction include revascularization, door-to-balloon time, age, gender, and presence of comorbidities (8). The mortality and morbidity data are limited because the patients who presented with myocardial infarction and had covid infection were not followed for an extended period. Also, the prognostic factors and the nature of myocardial

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infarction in patients with COVID-19 are unknown.

This study aimed to investigate the features of high-risk patients with COVID-19 who presented with myocardial infarction, the patients' one-year follow-up results, and prognostic disease factors.

MATERIAL AND METHOD

This study was designed as a retrospective observational cohort study. The patients admitted to Ankara City Hospital Emergency Polyclinic between June 2020 and December 2020 were investigated. Only patients diagnosed with high-risk myocardial infarction in the emergency room and with a positive PCR test for COVID-19 were enrolled. High-risk patients were defined as the patients who were referred to early invasive treatment (<24h) due to non-ST elevated myocardial infarction (NSTEMI) or ST elevated myocardial infarction (STEMI) according to recent ESC guidelines (9). The patients younger than 18 years and with active major bleeding were excluded.

Definition of Myocardial Ischemia

Only patients diagnosed with STEMI or NSTEMI, according to the fourth universal definition of myocardial ischemia, were included in the study (10). Moreover, the patients who didn't have full features of myocardial infarction but were highly suspect of myocardial infarction, such as sudden cardiac arrest, were enrolled.

Invasive Management of Myocardial Infarction

Patients were directly referred to the cardiac catheterization room from ER within 24 hours. The cardiac catheterization team consisted of two experienced cardiologists; one of them was the operator, two nurses, and one technician. All procedures were performed with local anesthesia. Intravenous midazolam was given if sedation was needed. Only intubated patients were under general anesthesia during the process. The femoral artery was used for arterial access. In patients with NSTEMI, selective left, and right coronary angiography was performed using the Judkins technique. Percutaneous coronary intervention (PCI) was performed if any culprit stenosis was detected. According to the ECG, selective coronary angiography for the artery assumed to have culprit stenosis was first performed in patients with STEMI. If it was feasible, PCI was performed. Then, selective coronary angiography was performed for another coronary artery to investigate additional stenosis. Only drug-eluting stents were used for PCI. After the procedures, a single Angio-Seal-VIP 8F vascular closure device (VCD) (Terumo Interventional Systems, Somerset, NJ, USA) was used to close femoral artery Access.

The coronary angiographies and procedure of PCI were re-evaluated retrospectively by two experienced cardiologists blinded to mortality data.

Follow-Up and Data Collection

All patients were followed at least one year after the first admission. Mortality data and medical records were retrospectively collected using the hospital's medical record software. Ankara City Hospital Local Ethics Committee approved this trial (07/07/2021, Project number 1941).

Statistics

Statistical analyses were performed with Statistical Package for Social Sciences program (SPSS) for Windows version 23 (IBM SPSS Inc., Chicago, IL). The variables were tested for Gaussian distribution with The Kolmogorov-Smirnov or the Shapiro-Wilk. Quantitative variables with Gaussian distribution were presented as mean and standard deviation, and the variables with non-Gaussian distribution were presented as median (minimum and maximum). All categorical data was stated as numbers and percentages. The Chi-square test was used to compare categorical variables. Independent sample t-test and Mann-Whitney-U test were used to compare the quantitative variables with Gaussian and non-Gaussian distribution, respectively. Logistic regression analyses were done to estimate the features related to all caused mortality. ROC analyses were performed to assess the predictive value of variables for mortality in one year. The level of 0.05 was determined as a cutoff value for statistical significance, and a lower p-value than the cutoff value was accepted as statistically significant.

RESULTS

Study Population and Groups

The study enrolled 80 patients with COVID-19 infection who performed invasive coronary angiography due to high-risk myocardial infarction between June 2020 and December 2020. The patients were divided into two groups according to the all-cause mortality during a one-year follow-up. Thirty-four patients (42.5%) died one year after the first admission. Thirty of them (88.2%) were in-hospital mortality.

Baseline Characteristics

Fifty-seven patients (71.24%) were male, and the mean age of the study population was 64.4 ± 13.4 years. Hypertension was the most common comorbidity, and it was present in 63 patients (78.8%). The patients who died during follow-up were older (68.8 ± 11.9 vs. 61.1 ± 13.6 years, p:0.01). Coronary artery disease and heart failure history were more common in this group (23 (67.65%) vs. 15 (32.61%), p: 0.002; 14 (41.18%) vs. 9 (19.57%), p: 0.035; respectively). Detailed baseline characteristics are presented in Table 1.

Results of Invasive Management

PCI was performed in 49 patients (61.25%). The median

Table 1. Baseline Characteristic.

	Mortality (-) (46)	Mortality (+) (34)	p
Male Gender; n (%)	30 (65.22%)	27 (79.41%)	0.166 ^{chi}
Age (Years; mean ± SD)	61.1 ± 13.6	68.8 ± 11.9	0.01* ^t
CAD; n (%)	15 (32.61%)	23 (67.65%)	0.002* ^{chi}
HT; n (%)	33 (71.74%)	30 (88.24%)	0.075 ^{chi}
DM; n (%)	9 (19.57%)	10 (29.41%)	0.306 ^{chi}
HF; n (%)	9 (19.57%)	14 (41.18%)	0.035* ^{chi}
CKD; n (%)	14 (30.43%)	14 (41.18%)	0.319 ^{chi}
CVE; n (%)	3 (6.52%)	3 (8.82%)	0.699 ^{chi}

CAD: Coronary Artery Disease; HT: Hypertension; DM: Diabetes Mellitus; HF: Heart Failure; CKD: Chronic Kidney Disease; CVE: Cerebrovascular Event; chi Chi-square test, t Independent Sample t-test, *p<0.05

Table 2. Results of Invasive Management.

	Mortality (-) (46)	Mortality (+) (34)	p
Culprit Vessel			
NCA; n (%)	5 (10.87%)	4 (11.76%)	0.62 ^{chi}
LMCA; n (%)	1 (2.17%)	0 (0%)	
LAD; n (%)	18 (39.13%)	17 (50%)	
Cx; n (%)	5 (10.87%)	5 (14.71%)	
RCA; n (%)	17 (36.96%)	8 (23.53%)	
Right dominance; n (%)	27 (58.7%)	24 (70.59%)	0.274 ^{chi}
	Mortality (-) (41)	Mortality (+) (30)	p
Door to Procedure Duration (Minute; min-max)	95 (18 - 1278)	83 (17 - 440)	0.183 ^m
Thrombus Grade, (min-max)	4 (1 - 5)	4.5 (0 - 5)	0.48 ^m
Syntax Score, (min-max)	11 (3 - 39)	21 (2 - 39.5)	0.015* ^m
PCI; n (%)	30 (73.17%)	19 (63.33%)	0.565 ^{chi}
Additional stenosis; n (%)	18 (43.9%)	17 (56.67%)	0.288 ^{chi}

NCA: Normal Coronary Arteries; LMCA: Left Main Coronary Artery; LAD: Left Anterior Descendant Artery; Cx: Left Circumflex Artery; RCA: Right Coronary Artery; PCI: Percutaneous Coronary Intervention; chi Chi-square test, m Mann-Whitney U-test, *p<0.05

door-to-procedure time was 107.5 minutes (17-1278). In 9 patients, any clinically significant stenosis was not found. In 22 patients, there was at least one hemodynamically significant stenosis, but the PCI was not feasible according to the operators' decision. The results of the coronary angiography and the comparison of the groups are listed in Table 2.

Laboratory Findings

The patients' laboratory findings are listed in Table 3. White blood count and the acute phase reactants, including ferritin, and IL-6, were significantly higher (9.8 (3.5 - 24.7) vs. 15.2 (6.1 - 28.8), p<0.001; 145 (13.9 - 1589) vs. 559.5 (8.4 - 6036), p<0.001; 21.1 (0 - 392) vs. 212.5 (12.5 -

1000), p<0.001; respectively) in the patients who died one year after admission. Also, the renal functions, such as creatine, BUN, and GFR, were impaired more in the same group (Table 3). LDH was significantly higher (299.5 (60 - 1818) vs. 924.5 (222 - 6906), p:<0.001) in these patients compared to the patients who survived in follow-up.

Regression Analyses and Predictive Values

Regression analyses showed that the levels of ferritin and LDH were independent factors related to mortality in patients with COVID-19 infection and myocardial infarction one year after the first admission (OR: 1.006, CI 95%: 1.001-1.01, p: 0.011; OR:1.005, CI 95%: 1.001-1.009, p:0.025; respectively). Detailed analyses are listed in Table 4.

ROC analysis showed that a higher ferritin level and LDH had a positive predictive value for one-year mortality. The cut-off value was estimated at 211 mcg/L for ferritin (AUC:0.762, sensitivity: 73.5%, specificity 63%, p:<0.001) and 492 U/L for LDH (AUC:0.863, sensitivity: 79.4%, specificity 80.4%, p:<0.001). Detailed information for ROC analysis is presented in Table 5 and Figure 1.

DISCUSSION

The primary finding of this observational study is that patients with myocardial infarction and COVID-19 infection have high mortality risk in admission and the following year. Most mortality events occurred in the first admission due to myocardial infarction. The second important piece of the results was no difference in the coronary angiography result except for syntax score between the two groups. However, the acute phase reactants were higher in the patients who met the mortality. Last, the levels of ferritin and LDH were independently associated with mortality and were found to be predictors for mortality.

A recent study investigated the intrahospital prognosis of patients with COVID-19 and out-of-hospital STEMI, and the mortality rates were reported at 15.2% (11). In the same study, the mortality rate was 78.5% for patients with in-hospital STEMI and COVID-19 (11). In our research, the intrahospital mortality rate was 38.75%, reaching 42.5% one year after the first admission. On the other hand, our study groups consisted of patients with STEMI or high-risk NSTEMI. They were referred to the catheterization laboratory from the emergency room, which means out-of-hospital MI, or intensive care units, which means in-hospital MI. Consequently, our cohort's high mortality seemed similar to this high-volume observational study.

COVID-19 pandemic was a unique event for physicians, cardiologists, and patients with heart diseases. So, the best medical approaches were investigated for myocardial infarctions, like every other illness during the pandemic.

Table 3. Laboratory Findings.

	Mortality (-) (46)	Mortality (+) (34)	p
Troponin (ng/L)	2520 (3-25000)	3977 (9-25000)	0.345 ^m
Peak Level of Troponin (ng/L)	13383.5 (7-25000)	16338.5 (67-25000)	0.454 ^m
Hemoglobin (g/dL)	13.8 ± 2.1	13.7 ± 1.6	0.821 ^t
Platelet (x10 ³)	258.5 (122-568)	280.5 (21.1-512)	0.386 ^m
White Blood Count (x10 ³)	9.8 (3.5-24.7)	15.2 (6.1-28.8)	<0.001 ^{**m}
Lymphocyte (x10 ³)	1.1 (0.3-4.2)	0.9 (0.2-6.4)	0.386 ^m
LDL (mg/dL)	98.2 ± 31.1	112 ± 39.4	0.084 ^t
HDL (mg/dL)	32 (15-63)	32 (11-49)	0.155 ^m
TG (mg/dL)	109 (41-485)	149 (61-756)	0.64 ^m
Creatine (mg/dL)	0.9 (0.5-3.3)	1.4 (0.6-10.3)	<0.001 ^{**m}
BUN (mg/dL)	35.2 (17-136)	69.5 (13-282)	<0.001 ^{**m}
GFR (%)	89 (17-5694)	48.9 (4.7-101)	<0.001 ^{**m}
Na (mEq/L)	138.5 (123-145)	138.9 (124-160)	0.361 ^m
K (mEq/L)	4.3 (3.2-6.5)	4.7 (3.5-59)	0.002 ^m
ALT (U/L)	33.5 (15-181)	42 (8-3344)	0.126 ^m
Ferritin (ng/mL)	145 (13.9-1589)	559.5 (8.4-6036)	<0.001 ^{**m}
IL-6 (ng/mL)	21.1 (0-392)	212.5 (12.5-1000)	<0.001 ^{**m}
LDH (U/L)	299.5 (60-1818)	924.5 (222-6906)	<0.001 ^{**m}

t Independent Sample t-test, m Mann-Whitney U-test, *p<0.05, **p<0.001

Table 4. Regression Analyses for Mortality.

	B	SE	OR	p	95% CI for OR	
Age (Years)	0.107	0.08	1.113	0.179	0.952	1.301 ^{BLR}
CAD	1.814	1.52	6.137	0.233	0.312	120.731 ^{BLR}
HF	2.963	2.032	19.35	0.145	0.361	1037.422 ^{BLR}
Syntax Score	-0.024	0.068	0.976	0.725	0.854	1.116 ^{BLR}
WBC (x10 ³)	0.262	0.168	1.299	0.12	0.934	1.807 ^{BLR}
GFR (%)	-0.039	0.027	0.962	0.145	0.913	1.013 ^{BLR}
Ferritin (ng/mL)	0.006	0.002	1.006	0.011*	1.001	1.01 ^{BLR}
IL-6 (ng/mL)	0.01	0.006	1.01	0.121	0.997	1.023 ^{BLR}
LDH (U/L)	0.005	0.002	1.005	0.025*	1.001	1.009 ^{BLR}
Constant	-17.248	8.819	0	0.051		

CAD: Coronary Artery Disease; HF: Heart Failure; WBC: White Blood Cell; GFR: Glomerular Filtration Rate; CI: Confidence Interval; OR: odds ratio; SE: Standart Error; BLR Binary Logistic Regression Model, *<0.05

Moreover, the guidelines and expert consensus documents about myocardial infarction in patients with COVID-19 were published in some countries (12). In our clinic, the invasive management for patients with myocardial infarction and COVID-19 was planned according to the recent myocardial infarction and revascularization guidelines (9, 13). Previous papers reported that physicians are intended more for non-

Table 5. Predictive Value for One-Year Mortality.

	Cut-off Value	Sensitivity	Specificity	AUC	SE	p	Lower Bound	Upper Bound
Ferritin (ng/mL)	211	0.735	0.63	0.762	0.054	<0.001	0.656	0.867
LDH (U/L)	492	0.794	0.804	0.863	0.041	<0.001	0.783	0.943

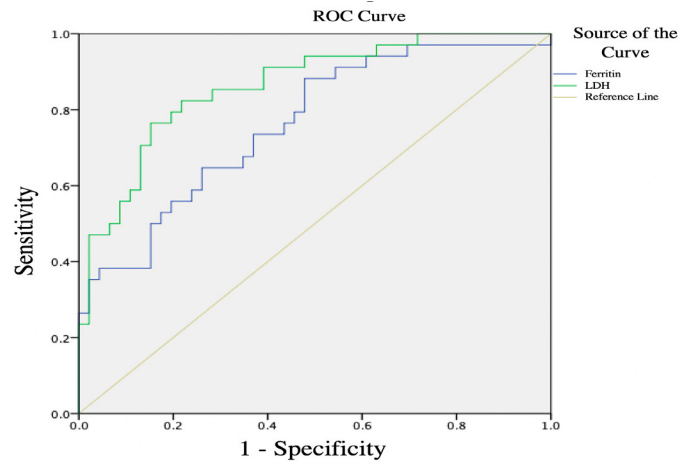


Figure 1. Relationship between mortality and levels of LDH and ferritin.

invasive treatment, although high-risk conditions, including cardiac arrest, are common among patients with myocardial infarction and COVID-19 infection. These findings are possible explanations for the excess mortality in this patient group (14). On the other hand, our study group's mortality rate was relatively high, even though we focused only on patients referred for invasive treatment.

Our study investigated the relationship between mortality, angiographic findings, baseline features, and biomarkers. Previous observational studies taught us that advanced age, male sex, comorbidities, and abnormal laboratory biomarkers are associated with fatal outcomes in patients with covid (15). Moreover, previous studies reported that a high GRACE score was a mortality predictor for patients with myocardial infarction and COVID-19 (16). We observed that a history of coronary artery disease and heart failure were more common in the patients who faced mortality in harmony with previous knowledge (15). There was no clinical difference in thrombus grade, but the syntax score was higher in these patients. However, only higher levels of LDH and ferritin were related to mortality in regression analyses. Previous studies showed that higher LDH levels were associated with a ~6-fold increase in odds of developing severe disease and a ~16-fold increase in odds of mortality in patients with COVID-19 (17). Similarly, higher ferritin levels, which reflect the magnitude of inflammation, predicted in-hospital mortality (18). In addition, renal functional tests at the first admission, including serum creatine, BUN, and glomerular filtration rate, were impaired in patients who died during follow-up. We interpreted this

finding to reflect the critical situation of these patients at the admission

This is the first study investigating the association between mortality and angiographic findings in patients who presented with myocardial infarction and had COVID-19 infection. In a recent survey, Montero-Cabezas et al. published an angiographic profile of the patients with COVID-19 referred for coronary angiography. They reported that MACE at 40 days was high (28%), primarily due to noncardiac death (19). Our study showed that only biomarkers of severe disease, LDH, and ferritin, were independently associated with mortality in a similar group. However, there was no difference in angiographic profile between study groups. This finding was mainly related to high non-cardiac mortality in our cohort. The observational data of the patients admitted with myocardial infarction is limited. Consequently, the results are significant.

Limitations

There are several limitations of this trial. First, the study population needed to be larger to make specific inferences. Second, the data were recorded from the medical recording software of our hospital. Patients were followed in different intensive care units, which could create heterogeneity for defining events and bias. Last, the mortality reason of patients who faced out-hospital mortality was recorded according to the knowledge of patients' relatives. So, the mortality reasons were not evident in this group. Further large-scale trials with longer follow-up durations will help understand the pathophysiology, prognosis, and differences of myocardial infarction patients with COVID-19.

CONCLUSION

The mortality rate in patients who presented with myocardial infarction and had COVID-19 is high despite the invasive management. History of coronary artery stenosis and heart failure presence were more common in patients who died during a one-year follow-up. Even though the syntax score is high in the patients who died during follow-up, only increased LDH and ferritin levels were independent predictors for mortality. A higher LDH level than 492 U/L predicts mortality with 79.4% sensitivity and 80.4% specificity in myocardial infarction and COVID-19 infection patients.

Ethics Committee Approval: Ankara City Hospital Local Ethics Committee approved this trial (07/07/2021, Project number 1941).

Informed Consent: Informed consent was provided from all patients who wanted participated in the study.

Authorship Contributions: Idea/Concept: CÇ, ÖÇK, Design: CÇ, ÖÇK, Supervision: SB, HAK, Data Collection

or Processing: FJ, Analysis or Interpretation: FK, CÇ, Literature Search: MOÖ, MAE, Writing: CÇ, ÖÇK, Critical Review: HTG, EA, References And Fundings:-, Materials:-.

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