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In-hospital clinical outcomes of COVID-19 patients with myocardial infarction

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ABSTRACT

Objective(s): Hospital outcomes for myocardial infarction are among the clinical conditions influenced by the spread of COVID-19. Patients with COVID-19 frequently experience cardiovascular complications, with challenges encountered in acute management. We assessed clinical presentation, incidence, clinical outcomes and angiographic findings of myocardial infarction in COVID-19 patients.

Methods: This study is a observational retrospective multicenter, medical diagram study was conducted on successive patients hospitalized with diagnosis of Covid-19 and myocardial infarction ,in two large referral hospitals with catheterization equipment and laboratories. COVID-19 infection was confirmed with reverse transcription–polymerase chain reaction assays of a nasopharyngeal sample or pattern of pulmonary parenchymal involvement in lung HRCT (approved by an expert respiratory or infection disease specialist). Data collected included patient demographics, comorbidities, electrocardiogram(ECG) and echocardiography results ,inpatient medication, treatment (fibrinolytic therapy, percutaneous coronary intervention (PCI) ,coronary artery bypass graft (CABG), vasopressor use, invasive mechanical ventilation), laboratory test results (leucocyte count, C-reactive protein , D dimer, BUN, Cr, and ferritin)and outcome(duration of hospitalization, revascularization success, in-hospital reinfarction and mortality).

Results: The most common comorbidities were hypertension (29, 58%), diabetes mellitus (21, 42%), dyslipidemia (14, 28%) and smoking (5, 10%). Fourteen patients (44.4%) were treated with PCI and 8 (19.5%) patients with fibrinolytic therapy as the initial reperfusion strategy. Revascularization was successful in 62% of patients. The median CRP level of patients died was 96, which was significantly more than the level (46) in discharged cases ($p<0.001$). Creatinine levels were also significantly higher in patients who died compared to those who were discharged ($p=0.008$).

Conclusion: The results of this study demonstrate upper mortality rate in patients with diabetes, kidney injury and high-level CRP, denoting the baseline clinical and laboratory data could be defined as prognostic markers in COVID-19 patients, especially while managing myocardial infarction with concurrent COVID-19 infection.

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Introduction

In December 2019, severe acute respiratory syndrome by a novel coronavirus disease (COVID-19) spread rapidly from Wuhan-China and became a pandemic (1). This pandemic caused

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significant and multifactorial stress on health care systems around the world. The most obvious pressure is related to the management of the respiratory syndrome, which is directly caused by covid-19 (SARS-CoV-2) (2). Till February 2021, COVID-19 has infected more than 110 million people and killed more than 2.5 million people. The most common symptoms of this disease are fever and cough (3, 4) . The elderly and those with underlying diseases including hypertension, chronic obstructive pulmonary diseases, diabetes and cardiovascular diseases moved more quickly towards ARDS, septic shock, metabolic acidosis, coagulation disorder and even death(5). Recent studies have related COVID-19 contamination with an augmented risk of ischemic stroke and acute myocardial infarction (AMI) (3, 4). In COVID-19 patients, coronary artery spasm, myopericarditis, pulmonary embolism, or stress-related cardiomyopathy exhibit symptoms comparable to STEMI.(5). In addition, there is a delay in presenting, referring, and transferring the patient to medical centers (6). Patients with STEMI and COVID-19 may have significant thrombosis due to increased coagulopathy, leading to non-optimal results of primary PCI (PPCI)(7). Despite extensive clinical evidence for thrombosis in COVID-19 infection, its exact cause is still unknown. Moreover, previous recent studies reported that patients with COVID-19 may experience major cardiac complications, including acute cardiac injury and myocardial infarction, which are characterized by elevated troponin levels. Additionally, this was associated with worsening the prognosis and a higher risk of in-hospital mortality in these patients (8). Pathological studies on patients with COVID-19 have shown disseminated microthrombi in these patients (9). These thrombotic events can lead to MI secondary to COVID-19. In a review study by Hamadeh et al. (2020), patients hospitalized with COVID-19 and STEMI in 4 hospitals in Italy, Lithuania, Spain, and Iraq were examined since February 1, 2020 to April 15, 2020. A total of 78 patients were examined in this study, including 49 men (63%), with an average age of 65 years. During hospitalization, 8 patients (10%) had acute respiratory distress syndrome and 14 patients (18%) required mechanical ventilation. 19 patients (24%) underwent primary PCI and 59 patients (76%) underwent fibrinolytic therapy. 13 patients (17%) required cardiac resuscitation and 9 patients (11%) died. Finally, the authors stated that their study was the largest study so far on COVID-19 patients with STEMI, contains 4 countries. They found a high rate of stent thrombosis, representing the necessity to adjust the management of STEMI patients according to COVID-19 patients (10). An early study in Wuhan, China, reported myocardial injury in 12% of patients with COVID-19 infection based on increased biological markers (9). So far, several cases of myocarditis caused by COVID-19 infection have been reported (11, 12). Another study by Popovic et al. (13) examined the echocardiographic and laboratory results of COVID-19 patients with STEMI and associated it with STEMI patients without COVID-19.The study results showed that LVEF and ST resolution higher than 70% were significantly lower in patients with COVID-19. Also, distal embolization after the procedure was significantly increased in the COVID-19 group. The TIMI grade after PCI was significantly higher in STEMI patients without COVID-19 than in the group with COVID-19. In general, systemic viral infection is associated with acute myocardial infarction and inflammation (14, 15) and in fact maybe a pathophysiological factor for plaque rupture and thrombosis. Despite the growing findings regarding the population with COVID-19, little is known about the specific clinical results and outcomes of patients with active COVID-19 infection with ST-elevation myocardial infarction (STEMI). In fact, data so far have been reported mainly on few cases of 72 patients in New York City with 18 deaths (9) and another of 39 patients from northern Italy with 28 deaths (16). In addition, it should be determined what effect COVID-19 has had on in-hospital MI outcomes. Therefore, we attempted to investigate the in-hospital clinical outcomes of COVID-19 patients with heart infarction.

Materials and Methods

The present study was retrospective and based on the information recorded in the patients' files and the total number of all eligible patients during a 1-year period during 2020. The study population included all patients with MI (including NSTEMI and STEMI) referred to the cardiac emergency department of Imam Reza and Qaim Hospital who also had COVID-19 infection. The diagnosis of COVID-19 was either based on the PCR of the nasopharyngeal samples of the patients or the CT scan of the patients whose findings are strongly in favour of COVID-19 in view of the pandemic and its confirmation was given by a pulmonologist or infectious disease specialists. The patients were followed for up to 2 years through post-discharge phone calls to evaluate the clinical conditions, the need for re-hospitalization, the status of symptoms, the regular use of drugs and death outside the hospital.

Demographic information, comorbidity, laboratory tests performed (WBC, CRP, D-Dimer, BUN, Cr, and ferritin), ECG results on arrival, echo findings (LVEF, right ventricular function,

presence of pericardial effusion and its severity), history of heart diseases (heart failure, ischemic heart disease, CABG or PCI, risk factors (HTN, DM, HLP and smoking addiction) were recorded. The information related to quantitative troponin level, coronary angiography, the extent of coronary thrombus and the number of involved vessels were collected.

The type of treatment given to the patient (thrombolysis, intraoperative procedures or referral for cardiac surgery), use of vasopressor or mechanical ventilation, need for CPR were recorded.

In-hospital outcomes were defined as mortality, success in revascularization or thrombolysis, incidence of re-infarction, incidence of stent thrombosis and the total length of hospital stay.

In case of thrombolysis, the success of thrombolysis was considered as >50% resolution in the ST segment, 60-90 minutes after administration. If PCI is performed, success is determined by TIMI Flow grade. The interval between door-to-wire crossing was recorded.

In addition, the relationship between the laboratory parameters evaluated in COVID-19 patients and the severity of pulmonary involvement with the extent of coronary artery involvement and in-hospital mortality were investigated.

Statistical method and sample size

After data collection, data were entered SPSS23 and statistical analyzes were performed. Descriptive findings were reported in the form of tables and graphs using appropriate dispersion and centrality indices. Quantitative data with normal distribution were defined by mean and standard deviation, and median and quartile range were used for information with non-normal distribution. Independent t-test was applied to compare parametric quantitative variables and Mann-Whitney U test analyzed non-parametric quantitative variables. If necessary, Fisher's exact test or Chi-square test was applied to compare qualitative variables among groups. In addition, to evaluate the effects of the confounding factors of the final outcome of the study, a suitable regression model was used. The significance level in all calculations was considered less than 0.05.Given that we had no assumed in-hospital clinical outcomes of COVID-19 patients with heart infarction. The sample size was n=50 in total, in two centers.

Results

Out of a total of 50 included COVID-19 patients, 34 patients (68%) had STEMI and the rest, NSTEMI. Fifteen (30%) out of 50 patients died during hospital admission and 70% were discharged. Among those with STEMI, 11 patients (26.8%) underwent PCI, 10 patients (24.4%) had CABG, 8 patients (19.5%) received thrombolytics, and 2 patients (5.3%) none of them, and only the anti-ischemic medication. Ten patients (24.4%) died in hospital. In those patients with NSTEMI, CABG was performed for 5 patients (29.4%), medical treatment for 4 patients (23.6%), and PCI for 3 patients (17.6%). Five patients (29.4%) died. Totally, 31 myocardial infarction patients (62%) had success in revascularization (including thrombolysis). For the extent of coronary artery involvement, 18 patients (36%) had 3VD, and 7 patients (14%) had 2VD.

Based on ECG findings, 10 patients with STEMI (66.6%) died. There was no significant difference in mortality between STEMI and NSTEMI (p=0.96). Also, 50% of deceased patients had EF less than 40%. 24 discharged patients (70.6%) had EF less than 40. The results of chi-square test showed no significant relationship between echo findings and mortality (p=0.40).

The data of the right ventricular function showed that 8 deceased patients (72.7%) had normal RV function. 25 discharged patients (71.4%) had normal RV function. The results of Fisher's test showed no significant relationship between RV function and mortality (p=0.62)

The median score of lung involvement in deceased patients was 18/26. The test results showed no significant relationship between the severity of lung involvement and mortality (p=0.07). The results of the Table (1) showed no significant relationship between D-dimer and mortality (p=0.29). The median CRP in patients who died was 96 with an average of 147.60±100.23, and 46 for discharged patients with an average of 58.81±53.16. The results of the Mann–Whitney test showed that the level of blood CRP in patients who died of heart infarction was significantly higher than that of discharged patients (p=0.001)

For the laboratory parameters, the median blood creatinine in the group of deceased patients was significantly higher than that of discharged heart infarction patients (p=0.008). No significant relationship was found between the level of white blood cells, lymphocytes, ferritin, urea and cTn, and mortality (p>0.05).

The findings presented that the average severity of lung involvement in 3VD patients was 75.23±9.6. The results of the Mann–Whitney test showed no relationship between the lung involvement and the vascular involvement (p=0.42) The funding displayed no significant relationship between the level of D-dimer and CRP, and the vascular involvement (p>0.05)(Table 1).

Table 1. Demographic and clinical findings of the study

VARIABLE	STEMI (N=34) Frequency	NON-STEMI (N=16) Frequency	P VALUE
AGE	12.14±64.35	8.66±67.62	0.34
Gender (Male)	24 (70.6)	10 (62.5)	0.80
History of diabetes	16(47)	8(50)	0.99
History of HTN	15(44.1)	11(68.7)	0.18
DLP history	9(26.5)	4(25)	0.98
Smoking	5(14.7)	1(6.25)	0.65
Opium consumption	6(17.6)	1(6.25)	0.40
Death rate			
Out-of- hospital death	5(14.7)	2(12. 5)	0.99
In- hospital death	10(29.4)	5(31.2)	0.98
Duration of hospitalization	6.5(4.0-10.25)	8.5(5.25-14.25)	0.21
Echo findings			
Left ventricular function			
LVEF>=40	11(32.3)	6(43.8)	0.47
LVEF<40	18(52.9)	9(56.2)	
Right ventricular function			
NL	20(58.7)	12(75)	0.62
REDUCED	9(26.5)	3(18.7)	
PE	1(0.2)	1(6.25)	
NO DATA	5(14.6)	1(6.25)	
INTERVENTION			
PCI	10(29.4)	3(18.7)	0.64
CABG	11(32.3)	4(25.0)	0.84
MEDICAL TREATMENT	9(26.5)	9(56.2)	0.08
Thrombolysis	4(11.8)	0(0)	0.38
TOTAL OF CAG	18(52.9)	7(43.7)	0.76
Severity of vascular involvement			
SVD	1(2.9)	1(6.25)	0.54
2VD	4(11.8)	1(6.25)	0.99
3VD	12(35.3)	3(18.7)	0.33
LM+3VD	0(0)	2(12. 5)	0.24
LM+2VD	1(0.2)	0(0)	>0.99
Severity of lung involvement	6(4-15)	20(6-21)	0.19
lab results			
D-DIMER (ng/ml)	1477(875.5-4385)	1566(200-6661)	0.52
Ferritin (ng/ml)	446(204-787.2)	684.5(319.2-7700)	0.23
WBC (1000/µL)	9.60(8.05-12.95)	9.30(7.65-10.90)	0.48
Cr (mg/dL)	1.10(0.90-1.55)	1.10(0.90-1.37)	0.67
Urea (mg/dL)	46.50(29.00-68.75)	57.50(47.50-66.25)	0.22
CRP (mg/dL)	49.70(44-101.50)	64(15.35-128.25)	0.44

Table 2. Clinical Conditions of patients after discharge

	Frequency
Readmission	2
Death	7
Symptom status: No symptoms	18
Symptom status: Symptomatic	6
Taking medicine: Yes	23
Taking medicine: No	2

The results showed that 7 patients died outside the hospital, of which 3 patients had non-cardiac diseases and the other 4 patients had cardiac causes. 18 patients had no symptoms and 23 patients took medicine (Table2).

While assessing the relation between the age and duration of hospitalization and the mortality, the results showed that the average duration of hospitalization in deceased MI patients was 9 days. Age and duration of hospitalization had no significant relationship with the mortality of patients ($p>0.05$) .

For gender and mortality of patients, the study results showed no significant relationship between gender and mortality ($p=0.18$) (Table 3).

For the risk factors of cardiovascular disease and mortality of patients, it can be said that a significant relationship was between the history of diabetes and mortality ($p=0.009$). However, the history of hypertension, dyslipidemia, smoking and opium use had no significant relationship with mortality ($p>0.05$) (Table 3).

Discussion

Our results showed that 30% of COVID-19 with myocardial infarction patients died. In a study by Rastad et al. on 2957 people over 18 years old in

Table 3. Relationship between risk factors and the mortality of heart attack patients

Variable	Discharge Frequency (%)	Death Frequency (%)	p-value
Hypertension			
Yes	17 (48.6)	9(60)	0.08
No	18 (51.4)	6(40)	
Diabetes			
Yes	11(31.4)	13(86.7)	0.009
No	24(68.6)	2(13.3)	
Dyslipidemia			
Yes	9(25.7)	4 (26.7)	0.89
No	26(74.3)	11 (73.3)	
Smoking			
Yes	5 (14.3)	1(6.7)	‡0.30
No	30 (85.7)	14(93.3)	
Opium			
Yes	5(14.3)	2(13.3)	‡0.30
No	30(85.7)	13(86.7)	
			0.18
Sex			
Male	27 (77.1)	7 (46.7)	
Female	8 (22.9)	8 (53.3)	

‡: Fisher's test was used.
* Chi-square test was used for comparison.

Alborz Province, 10% of the patients died(17). In a study by MRCP et al. (18) on people over 18 years old in England and Wales, mortality of COVID-19 patients was 25.3%. Patients with long-standing coronary artery disease as well as cases with risk factors for atherosclerotic cardiovascular disease may develop acute coronary syndrome during acute infections, which has been documented in clinical and epidemiological studies on influenza(19, 20) and other acute inflammatory disease (21). Such acute coronary events can be caused by an acute elevation in myocardial demand due to infections that accelerate myocardial infarction or injury. Also, circulating cytokines following severe systemic inflammatory stress cause atherosclerotic plaque rupture and instability. Likewise, patients suffering from heart failure may develop hemodynamic decompensation during stress caused by severe infectious diseases. Therefore, patients with underlying cardiovascular disease, which is more common in the elderly, are predicted to be at higher risk of opposing results and death throughout destructive and severe inflammatory reactions to COVID-19 than younger, healthier cases.

In our study, a significant relationship was observed between the history of diabetes and mortality. So the death rate was higher in patients with diabetes. A study by Guo W et al. indicated higher probability of in-hospital death in patients with DM. A study by Rastad et al. also showed that it is an important risk factor for mortality in COVID-19 patients. So that the risk of mortality in diabetic patients increased by 83% (68). A study by Ghou et al. using data of 174 COVID-19 patients in China found that diabetic patients without other comorbidities (n = 24) were at higher risk for severe pneumonia, death, as well as enzyme release related to tissue damage and excessive inflammation (22). Exposure of respiratory epithelium cells to high concentrations of glucose significantly increases the rate of infection and replication of the influenza virus (23). In our study, 68% of COVID-19 patients had STEMI. 26.8% of STEMI patients underwent PCI and 24.4% underwent CABG. Also, in our study, no relationship was observed between ECG findings and mortality Rattka Met al. (24) in a meta-analysis reviewed ten international studies with 50,123 patients. Similar to our results, the authors found no relationship between ECG findings and in-hospital mortality. A study by Garcia et al. (25) showed that 71% of 230 COVID-19 patients had STEMI. 71% of patients were PCI, 20% were medical, 3% were thrombolytic and 2% were CABG. In a study by Fizzah et al. (26), 15.4% of ECG findings were STEMi, which was 23.1% of PCI type. The mechanisms causing the presentation with STEMI and the associated higher arterial thrombus burden in COVID-19 patients are stillunknown.Regardingvenousthromboembolism, arterial thrombus is mostly due to platelet activation and endothelial dysfunction. Pre-COVID-19 data on influenza virus suggest that patients with acute respiratory infection are at significantly increased risk of atherosclerotic plaque rupture leading to myocardial infarction as a result of an acute inflammatory response and hemodynamic changes (19). SARS-CoV-2 infection causes a systemic inflammatory response that leads to endothelial activation and activation of platelets and the coagulation cascade (27). In our study, 50% of COVID-19 patients with myocardial infarction had an echocardiogram with LVEF less than 40. No significant relationship was between the patient's LVEF status and mortality. In a study by GU et al. (28), EF had no significant relationship with mortality. In a study by Daniel et al. (29), 16% of deceased patients and 14% of discharged patients had an echo with EF less than 40. In this study, no relationship was between echo status and mortality. In general, EF was not independently associated with mortality.The results of our study showed that blood level of CRP of patients who died was higher than that of discharged patients. In myocardial infarction patients, high CRP is predisposed to the formation of inflammatory cascade, which may finally lead to the rapid deterioration of COVID-19. A study by RYO et al. showed that blood CRP levels were significantly increased in deceased patients.Mortality risk ratio in patients with CRP level higher than 5.5 mg/L was 32% higher than CRP level less than 3 mg/L (30). In a study by Rastad et al., the increase in CRP level increases themortality risk of myocardial infarction patients by 14% (17). A study by Peng et al. on COVID-19 patients with heart infarction showed that the level of CRP in patients with critical condition(106.98) was significantly higher than that of patients with good general condition (34.34) (31). CRP is a sensitive and non-specific predictor of systemic inflammation. A patient's baseline hs-CRP level may be a simple and readily available measure that can help emergency care personnel identify patients with CVD who may be at high risk of death. Several studies have shown that increased CRP levels in patients with CVD, including those with acute coronary syndrome, ischemic stroke, and acute heart failure, are associated with their mortality (32, 33). The results of these studies, along with our results, suggest that CRP is a valuable biomarker for identifying patients with CVD at high risk of total in-hospital mortality. The mechanisms underlying the relationship between hs-CRP levels and the risk of atherosclerotic CVD death are still unknown. However, it is possible that high CRP levels reflect the extent of infarction and inflammation related to

the pathobiology of ischemic tissue damage(30, 34). For heart failure, it has been found that inflammatory markers such as TNF, interleukin (IL)-6 and CRP are increased in patients with congestive heart failure and related to the degree of heart failure (35). In our study, D-DIMER level had no significant relationship with the mortality patients. A study by Zaho et al. on PCI patients showed that for all-cause mortality, D-DIMER levels were significantly higher in patients who died than in those who survived in the population (36) Tang N et al.(37) in a study on 183 COVID-19 patients found that patients with abnormal coagulation results, significantly increased D-DIMER and fibrin, had a higher risk of death. In addition, Gao et al. found that D-DIMER levels are closely related to the occurrence of severe COVID-19 in adult patients (38). In accordance with these findings, it has been found that anticoagulation treatment reduced mortality in infected patients. It is associated with severe COVID-19 that significantly increases sepsis-induced coagulation criteria or D-DIMER levels (39). An important reason for the difference is the very low sample size in our study, in which the D-DIMER level was recorded for 11 people, and the power of the test is very low. The mechanism of how D-DIMER can predict mortality is unknown. D-DIMER levels reflect increased coagulation risk (40). Elevated D-DIMER levels are associated with some pathological processes, including thrombosis, plaque necrosis (41), infection (42), and cancer metastasis, which may make it an independent risk factor for cardiovascular disease mortality and other slow diseases. According to the results of our study, creatinine level was a significant predictor for the mortality of COVID-19 patients with myocardial infarction, which was directly related to mortality. Also, the level of urea was higher in patients with myocardial infarction who died than those who were discharged, but this difference was not significant. In a study by Rastad et al., the level of creatinine in deceased patients was 1.20 mg/dL, which was higher than discharged patients (0.1 mg/dL) (17). In a study by Martinol et al. on COVID-19 patients, the level of creatinine increased significantly in deceased patients (43). Increased serum creatinine and urea levels may indicate abnormal kidney function in COVID-19 patients, but may also indicate low glomerular filtration due to heart failure (44, 45). Angiotensin-converting enzyme 2 (ACE2) is a putative receptor for SARS CoV-2 (46). When the virus binds to ACE2, it prevents ACE2 from performing its normal function, leading to reduced renal perfusion and filtration, thus increasing serum creatinine and urea (47). In our study, in deceased patients, the level of white blood cells was high and lymphocyte level was lower, but no significant difference was found in discharged patients. A study by Rastad et al. (17) showed a high white blood cell count and a lower lymphocyte count in deceased patients. However, in patients who only suffered myocardial infarction, the number of white blood cells was not significant for mortality despite the high relative risk. In a study by Alamdari et al. (48), an increase in the total number of white blood cells along with a decrease in lymphocytes was shown as a prognostic marker of the disease. A decrease in the level of lymphocytes between COVID-19 patients was also a dependable index of poor prognosis, which has been reported in some other studies (14, 59). Lymphocytes regulate the inflammatory response and play an anti-atherosclerotic role, in which regulatory T cells, a subset of lymphocytes, may have an inhibitory effect on atherosclerosis (49). Previous studies have also shown low lymphocyte counts as an early marker of stress. Physiological and systemic collapse secondary to myocardial ischemia is mediated by cortisol secretion (50, 51). An increase in cortisol levels leads to a reduction in the relative level of lymphocytes (52).

Conclusion

In this study, it was shown that careful consideration of patients' medical history and background situations played an important role in the suitable management of COVID-19. History of diabetes had a significant relationship with mortality, with higher death rate in diabetic patients. It should be noted that the abnormal laboratory findings such as the increase in creatinine and CRP, along with the reduction in the number of lymphocytes, as well as the presence of risk factors such as diabetes, in COVID-19 patients can alert physicians to the possibility of higher mortality.

Limitations

One of limitations was that this study was two-center descriptive analytical study with a small sample size. Also, the information related to some variables was incomplete, which caused reducing the power of the tests.

Suggestions

According to limitations, a multicenter and prospective study is needed to collect patient information accurately and without missing data. Patients should be followed up to be able to identify factors affecting the mortality of patients in the long term with statistical models.

Ethical Approval

This study was approved on Oct. 10, 2021 by the Organizational Ethics Committee of the Faculty/Region of Mashhad University of Medical Sciences entitled "examination of in-hospital clinical outcomes of COVID-19 patients with cardiac infarction" No. 992330 and code IR.MUMS. MEDICAL .REC.1400.471.

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