Objectives: Coronavirus disease of 2019 (COVID 19) became a major public health issue, causing millions of deaths world wide. The burden of COVID 19 pandemics on access to medical care and the treatment of patients with chronic diseases and acute coronary syndromes (ACS) is not fully determined yet. In this study we aimed to compare the management and clinical outcomes of patients with ACS before and during pandemic.

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Methods: A total of 239 patients with ACS were enrolled into the study. Patients were divided into two groups. First group was prepandemic group consisted of patients admitted at January and February 2020, before the pandemic. Second group was consisted of ACS patients admitted through April and May 2020 during pandemic. Both groups were compared according to demographic properties, blood chemistry findings, angiographic features, revascularisation strategies and clinical outcomes.

Results: During pandemic period we observed an increase in total number of patient with ST elevation miyocardial infarction (STEMI) patients compared to prepandemic period (59(45%) vs 32 (29.6%) respectively). Initial high sensitive troponin and CK-MB levels were statistically higher in the pandemic group patients(1953 pg/ml vs 259 pg/ml for troponın I and 14 ng/ml vs 6ng/ml for CK-MB $p<0.0001$, $p=0.02$ respectively). TYPE 4a myocardial infarction due to stent thrombosis was more frequent in pandemic group relative top re-pandemic group (10 vs 0 $p=0.003$). Post procedural TIMI flow grade was lower in pandemic group and distal embolization and TIMI thrombus score were significantly higher in the pandemic group compared top re-pandemic group (, $p=0.001$, $p=0.02$,$p=0.002$ respectively). Due to limited cardiovascular surgery back up during April and May 2020, the number of patients who underwent bypass surgery was much lower compared to prepandemic period(27 vs 8, $p<0,0001$). However; there was no statistically significant difference in hospital mortality and short –term all cause mortality, among groups ($p>0.05$).

Conclusion: In this study, we observed that although clinical, laboratory, and angiographic features were worse in ACS patients admitted during the pandemic compared to pre-pandemic times, the mortality rate of ACS was similar in both times. It is important to keep coronary intensive care units and catheter labs open and fully-functioning during the pandemic.

Keywords: COVID-19, myocardial, infarction, mortality, thrombosis

Introduction

A novel corona virus; severve acute respiratory syndrome-corono virus 2 (SARS-CoV2) was identified by end of December 2019. The disease caused by this virus was named as "corona virus disease-2019" (COVID-19). The virus is severely contigous and the infection spread rapidly. On March 11 2020, World Health Organisation announced current situation as pandemic. In parallel, on March 10 2020, Turkish Ministry Of Health announced first case in Turkey.

COVID-19 is not only a pulmonary pathogen but also it affects cardiovascular system as well. It may affect on cardiovascular system by different ways such as myocarditis, stress induced cardiomyopathy, acute coronary syndrome and pulmonary embolisim (1-5). Still little is known how it affects heart and cardiovascular system. Potential mechanisims may include direct toxicity to myoctes, hypoxemia, endothelial damage and hypercoagulable state caused by COVID 19. (6,7)

COVID 19 causes systemic inflammation, and systemic inflammation may lead progression of subclinical cardiovascular diseases to overt disease (8). As known COVID 19 enters the cell via ACE 2 receptors. ACE 2 receptors are found in many tissues such as heart and vessels (9). This may explain direct cytotoxic effect of this virus on cardiovascular system (10). Other possible mechanisims are endothelial damage and dysregulation of Renin-Angiotensin and Aldesterone pathway (11).

Autopsy studies indicates that SARS-CoV2 infects endothelial cells. This invasion may cause inflamation at the endothelium resulting activation of coagulation pathway (7). As endothelium is the largest organ of the body, this may explain the magnitude of the hypercoagulable state (12, 13).

Apart from these interactions during natural course of life, people may suffer from ACS as well.

During strict lockdown periods people may have difficulty accessing medical contact and in addition people may be indisposed to seek medical care to lessen contact with others (14,15).

In a previous report it has been stated that the interval between the onset of symptoms and the first medical contact increased. It is hard to evaluate total ischemic time because of mimicry of symptoms such as dyspnea, chest pain and system mediated delays, evaluation of all patients as plausable COVID 19 (16).

It should be noted that mortality of untreated ACS is much higher than COVID 19 itself (15, 16). In this study we aimed to compare the management and clinical outcomes of patients with ACS before and during pandemic.

Methods

This is an observational single center study. 239 patients with ACS enrolled into the study. Patients with ACS admitted at January-Februrary 2020 were prepandemic group (group 1). ACS patient admitted through April and May 2020 were created as pandemic group (group 2) Angiographic features, blood chemistry findings, revascularization strategy, clinical outcomes, in hospital and short-term mortality were compared. Coronary angiographies were evaluated by two different experienced cardiologists who were blinded to the study. TIMI flow grade, TIMI frame rate and thrombus score were calculated according to Gibson et al (17, 18). Patient's demographic and labaratory datas were obtained from hospital electronic database. In-hospital clinical events and discharge all-cause death rates were noted from Turkish death notification system.

STEMI and NSTEMI diagnosis were made according to the current European Society of Cardiology (ESC) guidelines. The periprocedural pharmacotherapy and the revascularization technique used were left to the discretion of the primary operator according to the current guidelines. (19, 20) TIMI frame calculations and other angiographic evaluations were performed by two cardiologists that was blinded to other clinical data. Indication of invasive strategy for NSTEMI and unstable angina pectoris (USAP) was according to the current ESC guidelines at that time (19,20).

All cause mortality was used to assess in hospital and short term clinical outcomes.

Statistical Analysis

Distribution of data was assessed using the Kolmogorov-Smirnov test. Continuous variables are reported as either mean ± standard deviation or median- interquartile range- according to the distribution. Categorical variables are reported as numbers and percentages. Continuous variables were compared using independent sample T test on Mann Whitney U as appropriate. Event free survival curves were generated according to the Kaplan-Meier method. Differences in survival curves among the groups were assessed using the log-rank test. Cox regression analysis was used when calculating the hazard ratio for all-cause short-term mortality. A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 20 software (SPSS Inc., Chicago, IL).

Results

The study was composed of 239 patients with ACS who underwent coronary angiography. Of these patients 175 (72,9%) were male and mean age was 58,8 (12.2%) years. Chest pain was the major cause of admission in both groups. There was statistically non significant diference in terms cardiac arrest at admission. During the pandemic period, 1(0.8%) patient presented with cardiac

arrest, whereas in pre pandemic period 4 (3.7%) patients presented with cardiac arrest. Accompanying chronic diseases such as prexisting coronary artery disease, known malingnancy, history of bypass surgery were simillar among groups (all p>0.05). Altough stastistically non significant ejection fraction was lower in pandemic group (p=0.06). We observed an increase in STEMI cases increased during pandemic period, 59 (45%) patients presented during pandemic period with STEMI while only 32 (29,6%) patients presented with STEMI during prepandemic period (p=0.01). Conversely NSTEMI ACS underwent invasive strategy decreased during pandemic period compared to prepandemic period. Simillar decrease in USAP patients were also observed, during pandemic period 26 (19,8%) patients with USAP underwent coronary angiography whereas 31 (28,7%) patients presented with USAP at prepandemic period underwent invasive strategy. These findings may reflect patient selection bias for invasive strategy.

Initial blood chemistry findings are summaried at Table 2. Patients in pandemic group had statistically higher Troponin I, creatine kinase–myocardial band (CK-MB), low density lipoprotein (LDL) and aspartate aminotransferase (AST) (p<0.0001, p=0.02,p=0.001,p=0.003 respectively). Serum sodium concentration was statistically lower in pandemic group (p= 0.003). There was no statistically difference between all other laboratory parameters (p>0.05 for all).

The analysis showed no significant differences between groups in terms of culprit lesion localization, Syntax score and predilatation (p>0.05 for all). There was only one procedural death in both groups (p>0.05) (Table 3). Post dilatation after stent deployment was significantly lower in pandemic group (p<0.001).

Use of bare or drug eluting stents were simmilar in both groups. Initial TIMI frame count were simillar in both groups (p=0.84), altough statistically nonsignificant post procedural TIMI frame count was higher in pandemic group (p=0.053). Stent(s) used per patient, stent diameter and stent lenght were simillar among groups (*p*> 0.05 for all).

Post procedural TIMI flow grade 3 was significantly higher in prepandemic group (p=0.001). In pandemic group post procedural TIMI flow rate was statistically lower (p=0.001). Type 4 MI, distal embolization and TIMI thrombus burden were significantly higher in the pandemic group (p=0.003, p=0.02 ,p=0.002 respectively).

Twenty -seven (25%) patients underwent coronary artery bypass grafting (CABG) during prepandemic period but in contrast 8 (6.1%) patients underwent during pandemic group (p<0.001). The hospital length of stay was similar in both groups (p=0.22). There was no statistically significant difference in hospital mortality and short –term all cause mortality, in both groups (p>0.05)(Table 4).

Definite COVID-19 patients with a positive PCR result was analyed as an seperate group.

During the pandemic period 27 (19.8 %) of the patients had definite COVID 19 diagnosis confirmed by reverse transcription polymerase chain reaction (RT-PCR) PCR positive patients had higher mortality compared to the PCR negative patients admitted during the pandemic period and the total cohort, it was found that both in-hospital and short-term mortality were higher than those with PCR negative.(p=0.01,p=0.001,p=0.02,p=0.02 respectively)

According to Kaplan Meier and Cox proportional hazards regression analysis performed for short-term all-cause mortality, there was no statistically difference between the two groups (Hazard ratio [HR], 0.63; 95% confidence interval [CI]; 0.27-1.44; P=0.28) (Figure1).

Discussion

ACSs are main cause of death in devoloped countries. There are multiple reports about management of ACS during COVID-19 pandemic. As parallel to our findings these reports indicate delayed presentation and prolonged ischemic time due to social distancing and system mediated delays.

In our study we observed lower post procedural TIMI frame count and TIMI flow grade in pandemic group. Distal embolisation, TIMI thrombus score and Type 4 MI was also higher in pandemic group. Our findings are in parallel with Choudry et al (21)These changes may reflect thrombotic mileu caused by COVID 19 as well as prolonged ischemic time despite appropriate door to balloon durations. SARS-CoV-2 may elict an severve pro-inflammatory and cytokine storm leading to vascular inflammation and plaque rupture. This situation is associated with a hypercoagulable state and platelets activation leading high TIMI thrombus scores (22) Our study demonstrates also high incidence of distal embolisation and TIMI thrombus score in pandemic group.

Previous studies have reported decreased STEMI cases (23). In contrast to this finding we observed an increase of STEMI cases during pandemic period. This was caused by interruption of primary percutenous interventions at nearby hospitals due to high hospitalisation demand for COVID 19. A previous survey reported that only 64% of cath labs remained open during the COVID-19 pandemic across United Kingdom (24). During that time many of intensive coronary care unit beds were turned into COVID 19 wards. Patient transfer from other hospitals and emergency service protocols for COVID 19 evaluation inadvertedly resulted prolonged ischemic time in ACS patients. In majority of health centers suspected ACS patients were evaluated with CT scan and echocardiography for COVID-19 triage. These protocols resulted cancelation direct transfer of patients to the catheterization labaratory (14). In addition, that noteworthy ST-segment changes may be observed in patients with COVID-19 in the absence of significant stenosis in the coronary arteries. This may be caused by hypoxemia and coexixsting inflammotory state, leading to misdiagnosis of ACS. That may cause diagnostic challenges during triage (14) In contrast to

NSTEMI and USAP, STEMI has a louder natural course and more definite ECG findings. Therefore it is less likely to misdiagnose STEMI as nonspesific ST segment changes during course of COVID 19 disease (25)

If long delays to perform the PPCI are expected or inabilty to perform PPCI pharmacoinvasive strategy or early fibrinolytic therapy may be preffered as a reasonable approach. Pharmacoinvasive strategy may aid to gain time to complete screening for COVID-19. Besides that advantage it should be kept in mind that thrombolitic theraphy is not free of complications, the role of secondary hemostasis during the course of COVID-19 is complex and not yet well defined. In patients with STEMI and high-risk NSTEMI defined according to ESC guidelines PPCI or early invasive strategy should be choice of threatment (26, 27).

We observed higher trombus load and more angiographically visible distal embolisation in pandemic group. Proecdural charecteristics were also different between groups. Post dilatation after stent deployment rate was significantly lower in pandemic group. This situation can be explained in several ways. First, expecially in heavily thrombotic lesions agressive balloon dilataion may cause more distal embolisation and coronary slow flow therefore operators may be conservative for post dilataion (28). Second, when current situation is taken into account operators concern and intention to end up procedure as fast as possible may be another explanation. ACS patients treated with manual thrombectomy were simillar between groups. This may be becaouse of operators choice to end up procedure and fear of increased cerebrovascular accident as well. TIMI flow grade is a well defined method to assess coronary artery flow (17, 18). In our study we observed that post procedural coronary artery flow was slower compared to prepandemic group patients. Post procedural TIMI flow grade was lower in pandemic group. In a previous report Showkathali et al reported simillar findings (29). This findings may be a reflection of thrombotic mileu caused by COVID 19. In addition prolonged total ischemic time despite normal door to balloon time can be strong factor to devolop thrombotic coronary artery lesions. Ideal antiplatelet theraphy and anticoagulant regime for ACS patients during pandemic period is not known.

In our center our door-to-balloon times were not different from prepandemic period. All patients were accepted as PCR positive therefore no additional tests were done for COVID 19 evaluation prior to PPCI. Catheterization labaratory personel were chosen from the most experienced personnel and procedures were performed under strict safety rules.

Stent thrombosis is the most feared complication of interventional cardiology. There are numerous cassification of stent thrombosis according to duration after stent deployment (30). Stent thrombosis is complex and have multifactorial mechanisims and risk factors. In our study we observed

increased incidence of stent thrombosis in pandemic group. COVID-19 causes a predisposistion to coagulation by different mechanisms (31,32). The cytokine storm that occurs 5 to 7 days after the onset of symptoms triggers hypercoagulable state and platelet activation mediated by interleukin-6 and tissue factor. In addition virus itself may directly damage the endothelium by binding via ACE 2 receptors and promotes permanent inflammation and Virchow triad (33,34). Under current conditions many countries have to do strict limitations to protect people from COVID-19. This limitations may block the patients to reach their routine prescriptons and impair drug adherence as well (35). Premature discontinuation of antiplatelet drugs is a well known risk factor for stent thrombosis (36). Of note in our study two of our stent thrombosis patient was PCR positive. Those patients presented with subacute stent thrombosis namely one week after stent implantation. Other patients with stent thrombosis were previously stented for ACS treatment and were within their first year of stent implantation.

In our study there was a significant difference between groups in bypass surgery group. At the prepandemic period 27 patients underwent bypass surgery whereas in pandemic group only 8 patients underwent bypass surgery. During pandemic period all elective surgeries were postphoned, in addition our cardiovascular surgery intensive care unit was occupied by intubated COVID 19 patients during that time.

Altough bypass surgery reduces long term mortality in multivessel disease patients bypass surgery it self may increase in-hospital mortality as well (37). This may explain higher but statistically nonsignificant inhhospital mortality during prepandemic period. Interestingly during prepandemic period we had four patients with cardiac arrest under cardiopulmonary ressicutation but in pandemic group we had one patient like this. Altough statistically nonsignificant this situation may have an effect on inhospital mortality difference between groups.

PCR positive COVID 19 patients were seperately evaluated. Both in hospital and short-term (six months) mortality were statistically higher in PCR positive patients compared to PCR negative patients and prepandemic period. Our findings are in parralel with Solano-Lopez et al. They reported that COVID 19 is an independent risk factor for poor STEMI prognosis and associated with higher in hospital mortality (38).

Limitations

The major limitation of our study is lack of total ischemic time data from pandemic period. Another limitation of our study is that our series comes from an observational, retrospective evaluation, which is certainly susceptible to selection bias. Moreover, the small sample size and the short-term follow-up did not allow us to draw any conclusions on hard endpoints.

Conclusion

In conclusion, COVİD-19 pandemic ACS patients had significantly higher baseline troponin and CK-MB levels most likely reflecting the prolonged total ischemic time. Second, in terms of procedural characteristics, stent thrombosis at admission, TIMI thrombus score were significantly higher and the final TIMI flow was lower at pandemic period. These findings may also be related to the higher thrombus burden. Optimal antiplatelet theraphy and anticoagulant regimes should be clarified for COVID 19 patients. Importantly the number of patients who underwent bypass surgery was much lower compared to pre pandemic period.

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