

COVID-19 in Iran: Clinical Presentations and Outcomes in Three Different Surges of COVID-19 Infection

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Short report

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Abstract

Background: A few studies compared the characteristics and outcomes of COVID-19 patients during the first and second surges of the disease. We aimed to describe the clinical features and outcomes of COVID-19 patients across the first, second, and third surges of the disease in Tehran, Iran.

Method: We conducted a retrospective cohort study of patients with COVID-19 admitted to Sina hospital of Tehran, Iran, during three surges of COVID-19 from February 16 to October 28, 2020.

Result: Surge 1 patients were younger with more prevalence of hypertension. They also presented with significantly higher oxygen saturation, systolic blood pressure, and respiratory rate on admission. Patients had higher levels of neutrophil to lymphocyte ratio, Urea, CRP, and ESR, in surge 2. The incidence of dyspnea, chest pain, and neurological manifestations followed a significant increasing trend from surge 1 to surge 3. There was no difference in severity and in-hospital mortality between the surges. However, the length of hospital stays and acute cardiac injury (ACI) was less in surge 1 and acute respiratory distress syndrome (ARDS) in surge 2 than in other surges.

Conclusion: patients did not significantly differ in disease severity, ICU admission, and mortality between surges; however, length of hospital stay and ACI increased during surges, and the number of patients developing ARDS was significantly less in surge 2 compared to other peaks.

Introduction

Iran has been one of the most affected countries during the COVID-19 pandemic in the middle east, experiencing the COVID-19 outbreak with 3,180,092 confirmed cases and 83,985 deceased cases till June 29, 2021 [1]. During some periods of COVID-19 outbreaks, Iran was ranked the third and second country worldwide regarding the total number of patients and mortality, respectively [2]. Up to now, this country has faced different surges of COVID-19 outbreak. Previous observations have reported COVID-19 mortality association with several risk factors and comorbidities such as diabetes, hypertension, cancer, cardiovascular disease, chronic kidney disease, and other chronic diseases [3, 4]. Thus evaluating the epidemiological characteristics of COVID-19 and specifying the underlying comorbidities of SARS-CoV2 infected patients could be of great importance to help public health officials, decision-makers, and clinicians to make pragmatic strides towards reducing the burden of COVID-19 and the subsequent control of the pandemic during upcoming surges.

This study aims to describe the demographic features, comprehensive clinical and laboratory parameters, and in-hospital outcome differences across the first, second, and third surges of COVID-19 hospitalized patients during a large cohort study in Iran.

Methods

All participants provided informed written consent before enrolled in the study, and the ethics committee of the Tehran University of Medical Sciences was approved for the study (IR.TUMS.VCR.REC.1399.018.). Our study has been performed in accordance with the declaration of Helsinki.

This retrospective cohort study was performed in the Sina Hospital, a COVID-19 referral center affiliated with Tehran University of Medical Sciences (TUMS) in Tehran, Iran, From February 16 to October 28, 2020. We included patients over 18 years of age with the diagnosis of COVID-19 who fulfilled one of the two following criteria: (i) PCR -confirmed Covid-19 oropharyngeal or endotracheal swab specimens. (ii) Highly suspected COVID-19 patients according to the World Health Organization's interim guidance [5] and Iranian national committee of COVID-19 [6], including patients with the signs of COVID-19 involvement in their chest computed tomography scan (presence of ground-glass opacity, either isolated or with consolidation), which cannot be fully defined by volume overload, lobar or lung collapse, or nodules along with the history compatible with COVID-19. Demographic data, comorbidities, clinical presentations, vital signs on admission, and laboratory data were extracted from patients' electronic medical records. All patients were followed up for in-hospital complications, severe COVID-19 manifestations, and in-hospital mortality across their admission period. We classified patients into three surges based on admission time: surge 1 (February 15 to April 30, 2020), surge 2 (May 1 to August 30, 2020), and surge 3 (September 1 to October 30, 2020). Disease severity, comorbidities, and in-hospital outcomes were defined based on previous studies [7, 8].

Categorical variables presented as numbers (%) and compared using the chi-square and chi-square post hoc test, in which we assumed $P \leq 0.00833$ as statistically significant according to the Bonferroni correction. The normality of distribution for numerical variables was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables with normal distribution were presented as mean \pm standard deviation and compared using the one-way ANOVA test. In contrast, variables with skewed distribution were presented as median [interquartile range] and compared using the Kruskal-Wallis test. All statistical analyses were performed using SPSS Statistics for Windows, Version 21, and $P < 0.05$ was considered statistically significant.

Results

Demographic and baseline characteristics

As of February 16, 2020, 19722 patients were screened and 3309 patients were admitted with COVID-19 diagnosis. A total of 649(19.6%) patients were deceased during this cohort, of whom 387(59.6%), 149(23.0%), and 113(17.4%) patients were admitted in the intensive care unit (ICU), emergency department, and wards respectively. The majority of deceased patients (160 out of 649 (24.6%)) were in the 70–80 age group. In this study we excluded patients with the lack of key information in their medical records. Finally, 1323 patients were included representing 667, 489, and 167 patients during surges 1, 2, and 3. Baseline characteristics of patients during the three surges are presented in Table.1. During the first, second, and third surges, the mean ages of hospitalized patients were 57.6 ± 16.3 , 61.0 ± 16.6 , and

60.7 ± 16.6, respectively (P: 0.001). Comparing the three waves, men constituted the majority of COVID-19 cases (61.1%) during our study period; however, patients did not differ between the three surges with similar gender and body mass index (BMI). Hypertension was the most common comorbidity presenting in 595 patients (45.0%) in all three surges, followed by diabetes mellitus (29.7%) and a history of cardiac disease (23.3%). The prevalence of comorbidities did not differ significantly between the surges except for hypertension (P: 0.015), and the proportion of patients with hypertension was significantly lower in surge 1 in comparison with surges 2 and 3 (P < 0.0083).

Clinical presentation

Clinical presentation symptoms including cough, dyspnea, fever, myalgia, and arthralgia were the most common among hospitalized patients with COVID-19. Apart from fever, headache, sore throat, and loss of consciousness, the prevalence of all symptoms differed significantly between the surges (P < 0.001 except for cough P: 0.001). After Bonferroni's post hoc analysis, we found out that the incidence of dyspnea, myalgia and arthralgia, nausea and vomiting, chest pain, and neurological manifestations followed a significant increasing trend from surge 1 to surge 3 (P < 0.008). Cough and abdominal pain were more frequent in surge 1 and then significantly decreased during surge 2.

Clinical and laboratory findings

The vital signs and laboratory parameters on admission are presented in Table.1. The heart rate, systolic blood pressure (SBP), respiratory rate, and oxygen saturation of patients were significantly different across the surges (P < 0.001). Application of Bonferroni post hoc test showed that patients in surge 1 presented with significantly lower SBP, lower respiratory rate, and higher oxygen saturation levels on admission when compared to surges 2 and 3 (P < 0.008). Regarding laboratory parameters, a significant difference was observed in neutrophil (P: 0.003) and lymphocyte count (P < 0.001), neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systemic immune-inflammation index (SII), urea, blood urea nitrogen/creatinine ratio, serum potassium, calcium, phosphorus, and magnesium levels of patients between the surges (P < 0.001). Additionally, serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alkaline phosphatase (ALP) (P < 0.001), hemoglobin (P: 0.008), sodium (P: 0.009), and aspartate transaminase levels (P: 0.010) differed significantly in patients hospitalized across the three surges. Bonferroni post hoc analysis demonstrated that patients in surge 2 were found to have significantly higher platelet to lymphocyte ratio, SII, and urea than the two other surges (P < 0.008). Patients from the first wave differed remarkably from those of the two subsequent surges of disease in that they had lower calcium, ESR, and lactate dehydrogenase (LDH) serum levels (P < 0.008).

In-hospital complications and outcomes

The median length of hospital stay during surges 1, 2, and 3 was 4 days (interquartile range (IQR): 2–7), 6 days (IQR: 3.0–9.0), and 6 days (IQR: 4.0–9.0), respectively (P < 0.001). The length of hospital stay was shorter during surge 1 than two other surges (P < 0.008). The number of patients requiring invasive ventilation did not differ between the three waves (P: 0.149). We presented the number of admitted, severe, and deceased patients based on 1-week intervals in Fig. 1. The mortality rate during surges 1 to 3

was not significantly different, and the number of deceased cases was 114(17.1%), 91(18.6%), and 30(18%), respectively ($P < 0.798$). There was no difference in the percentage of patients developing severe COVID-19 with 896 (67.7%) of patients in surge 1, 437(65.5%) of patients in surge 2, and 349(71.4%) of hospitalized patients during surge 3 ($p = 0.094$). There were statistically significant differences regarding acute respiratory distress syndrome (ARDS) ($P < 0.022$) and acute cardiac injury (ACI) development ($P: 0.017$) between patients during three surges, which presented based on 1-week intervals in Fig. 2. The number of patients developing acute kidney injury (AKI), acute liver injury (ALI), and multi-organ damage were not significantly different between the surges. After Bonferroni's post hoc analysis application, we observed that during surge 2, patients were less likely to incur ARDS than patients hospitalized during surge 1 and 3 ($P < 0.008$).

Discussion

The most prominent finding in this study was the difference in age, clinical presentations, length of hospital stay, developing ARDS, and ACI in three different surges of COVID-19 infection. On the other hand, there was no difference regarding disease severity and in-hospital mortality among three different surges.

Older people have been speculated to be more vulnerable to COVID-19 infection and its further complications [9]. The mean age of hospitalized patients in our study was 59.2 ± 16.5 . Mean age was lower in our study during the first wave, which is in contrast with the findings of Atkin et al., reporting lower mean age of patients during the second wave [10]. We believe that this may be attributed to different study populations and smaller sample sizes in our study, while both studies have included only admitted patients.

The median BMI in our study was 27.4 ± 4.7 kg/m² and was lower than that reported in New York (30 kg/m²) [11]. It has been reported that obesity is associated with worse outcomes among COVID-19 patients [12], and a lower BMI in the current study might have been protective. We demonstrated that hypertension, diabetes mellitus, and cardiac disease were the most common comorbidities among patients. Underlying diseases are associated with higher risk severe COVID-19 and its complications [13]. Vahidy et al. reported that the number of COVID-19 hospitalized patients with hypertension was significantly higher during surge 1 of the COVID-19 pandemic in Houston, which is in alignment with our results [14].

The prevalence of dyspnea, myalgia and arthralgia, nausea and vomiting, chest pain, and neurological manifestations significantly increased from surge 1 to 3. Gastrointestinal symptoms with more incidence in the second wave were reported in previous observations [15]. Patients admitted during surge 1 had higher oxygen saturation with lower SBP and respiratory rate than surges 2 and 3. The results demonstrate that the non-respiratory presentations of COVID-19 are increasing over time. The SARS-CoV-2 virus can infect various organs using angiotensin-converting enzyme (ACE2) receptors to enter cells

[16]. Therefore, during this pandemic era, extra-pulmonary symptoms should be given more attention by physicians

Lower than normal absolute lymphocyte count, higher neutrophil to lymphocyte ratio, and elevated than normal CRP, ESR levels are significantly associated with a higher mortality rate in hospitalized COVID-19 patients [17]. Besides, elevated serum levels of creatinine and urea were correlated with hospitalized COVID-19 non-survivors [18]. Our patients differed significantly in neutrophil to lymphocyte ratio, Urea, CRP, and ESR with higher levels of these laboratory markers in surge 2.

Patients who developed ACI were reported to be older with more comorbidities such as HTN and DM, lower lymphocyte count, and higher ALT levels, leukocyte count, and hs-CRP on admission compared to those who did not develop ACI [19]. Similarly, we found that as the number of patients with hypertension rose from surge 1 to surge 3, more patients developed ACI and had lower lymphocyte count than surges 1 and 2. Furthermore, developing ARDS is also associated with elevated cardiac troponin levels and worsened clinical outcomes [20]. We similarly found that the more patients developed ARDS from surge 1 to 3, the more they developed ACI. However, disease severity, in-hospital mortality, and the number of patients receiving invasive mechanical ventilation in our study did not differ across the surges, and the overall in-hospital mortality rate was 17.8% during our study period. Some previous studies demonstrated a lower disease severity, need for invasive mechanical ventilation, and mortality during the second wave [10]. The rate of ICU admission was 16.4% in our study, and patients did not differ in need of intensive care support. Our results are in line with the findings of Atkin et al., reporting no difference in ICU admission during the first and second wave [10].

The strength of the current study is the comparison between three surges of COVID-19 patient's characteristics and outcomes for the first time in Iran as a country with a high burden of COVID-19 pandemic. Several limitations to the current study need to be addressed. First, the present study is an observational study with possible inherent biases. Second, it is a single-center study on the Iranian population, and future multicenter studies with larger sample sizes and different ethnicities are needed.

Abbreviations

ACE2: angiotensin-converting enzyme

ACI: acute cardiac injury

AKI: acute kidney injury

ALI: acute liver injury

ALP: alkaline phosphatase

ALT: alanine transaminase

ARDS: acute respiratory distress syndrome

AST: aspartate aminotransferase

BMI: body mass index

BUN: blood urea nitrogen

CRP: C-reactive protein

DBP: diastolic blood pressure

ESR: serum erythrocyte sedimentation rate

hs-cTnI: high sensitive cardiac troponin I

ICU: intensive care unit

IQR: interquartile range

LDH: lactate dehydrogenase

SBP: systolic blood pressure

SII: systemic immune-inflammation index

Declarations

Ethics approval and consent to participate

All participants provided informed written consent before enrolled in the study, and the ethics committee of the Tehran University of Medical Sciences was approved for the study (IR.TUMS.VCR.REC.1399.018.).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests

Funding

Authors' contribution

AH: data acquisition

MP: drafted the manuscript

SK: desing of the work, analysed the data, revised the manuscript

HF: design of the work, revised the manuscript

ME: data acquisition

SKS: data acquisition

MT: data acquisition

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Tables

Table 1. Baseline characteristics and in-hospital outcomes of COVID-19 during different surges.

Characteristic†	Total (N=1323)	Surge 1 (N=667)	Surge 2 (N=489)	Surge 3 (N=167)	P*
Demographics					
Age (year)	59.2±16.5	57.6±16.3	61.0±16.6	60.7±16.6	0.001
Sex	Female	515(38.9%)	249(37.3%)	197(40.3%)	0.473
	Male	808(61.1%)	418(62.7%)	292(59.7%)	
BMI (kg/m ²)	27.4±4.7	27.5±4.9	27.3±4.6	27.4±4.6	0.917
Comorbidities					
Hypertension	595(45.0%)	274(41.1%)**	237(48.5%)	84(50.3%)	0.015
Diabetes mellitus	393(29.7%)	197(29.5%)	145(29.7%)	51(30.5%)	0.968
Cardiac disease	308(23.3%)	147(22.0%)	122(24.9%)	39(23.4%)	0.512
Cerebrovascular disease	58(4.4%)	22(3.3%)	28(5.7%)	8(4.8%)	0.133
Chronic lung disease	82(6.2%)	50(7.5%)	22(4.5%)	10(6.0%)	0.112
Malignancy	59(4.5%)	28(4.2%)	25(5.1%)	6(3.6%)	0.641
Chronic kidney disease	63(4.8%)	33(4.9%)	23(4.7%)	7(4.2%)	0.971
Symptoms					
Fever	721(54.5%)	354(53.1%)	271(55.4%)	96(57.5%)	0.518
Cough	825(62.4%)	447(67.0%)**	273(55.8%)**	105(62.9%)	0.001
Dyspnea	799(60.4%)	361(54.1%)**	325(66.5%)**	113(67.7%)	<0.001
Myalgia and arthralgia	637(48.1%)	273(40.9%)**	261(53.4%)**	103(61.7%)**	<0.001
Headache	223(16.9%)	100(15.0%)	89(18.2%)	34(20.4%)	0.154
Nausea and vomiting	354(26.8%)	133(19.9%)**	151(30.9%)**	70(41.9%)**	<0.001
Sore throat	57(4.3%)	31(4.6%)	16(3.3%)	10(6.0%)	0.272
Chest pain	167(12.6%)	62(9.3%)**	70(14.3%)	35(21.0%)**	<0.001
Abdominal pain	227(17.2%)	160(24.0%)**	44(9.0%)**	23(13.8%)	<0.001
Neurological manifestations	110(8.3%)	38(5.7%)**	42(8.6%)	30(18.0%)**	<0.001
LOC	83(6.3%)	35(5.2%)	35(7.2%)	13(7.8%)	0.288

Vital signs on admission					
Heart rate	91.2±24.0	88.6±16.4	93.7±32.5	93.4±15.5	<0.001
SBP (mmHg)	126.3±21.2	123.8±20.5**	128.3±21.8	128.7±21.4	<0.001
DBP (mmHg)	76.6±12.9	75.8±11.7	76.9±13.4	78.2±15.0	0.131
Respiratory rate	21.0±5.7	19.8±5.6**	22.3±5.9	21.2±4.6	<0.001
Temperature (°C)	37.2±0.9	37.2±0.9	37.2±0.9	37.1±0.9	0.706
Oxygen saturation (%)	89.2±8.1	90.7±7.4**	87.7±8.8	88.1±7.7	<0.001
laboratory data on admission					
WBC (x10 ⁹ /L)	6.9[5.2-9.5]	6.6[5.2-9.5]	7.4[5.3-9.5]	7.2[5.1-9.6]	0.338
Neutrophil (x10 ⁹ /L)	5.3[3.7-7.7]	4.8[3.6-7.3]	5.9[3.9-8.1]	5.6[3.7-7.5]	0.003
Lymphocyte (x10 ⁹ /L)	1.1[0.8-1.6]	1.2[0.9-1.7]	1.0 [0.7-1.4]	1.1[0.8-1.5]	<0.001
Platelets (x10 ⁹ /L)	194.0[151.0-265.5]	191.0[150.0-258.0]	203.0[157.0-282.7]	192.5[152.0-262.2]	0.094
Neutrophil-to-lymphocyte ratio	4.5[2.7-8.1]	3.8[2.5-6.5]	5.9[3.4-10.1]	4.7[3.0-7.0]	<0.001
Platelet-to-lymphocyte ratio	173.1[119.7-259.3]	154.4[114.0-216.1]	206.8[138.3-336.1]**	178.1[121.7-259.9]	<0.001
SII	889.6[498.5-1745.4]	762.1[445.8-1380.9]	1221.4[610.2-2607.7]**	913.2[518.1-1714.6]	<0.001
Hemoglobin (g/dL)	13.5[12.1-14.9]	13.7[12.4-15.0]	13.3[11.8-14.6]	13.5[12.0-14.8]	0.008
Urea (mg/dL)	34.0[24.0-53.0]	32.0[23.0-49.0]	39.0[27.0-60.0]**	34.0[25.7-48.0]	<0.001
BUN/creatinine ratio	14.7[11.2-19.5]	13.9[10.7-18.3]	15.9[12.2-20.7]	14.7[11.3-18.6]	<0.001
Creatinine (mg/dL)	1.1[0.9-1.3]	1.1[0.9-1.3]	1.1[0.9-1.3]	1.1[0.9-1.3]	0.157
Sodium (mmol/L)	136.3[133.1-139.4]	136.0[132.8-139.4]	137.0[133.8-139.9]	135.9[132.7-138.2]	0.009
Potassium (mmol/L)	4.3[4.0-4.7]	4.3[3.4-4.6]	4.4[4.0-4.9]	4.4[3.9-4.7]	<0.001
Calcium (mmol/L)	8.8[8.3-9.2]	8.7[8.2-9.1]**	8.8[8.4-9.2]	8.8[8.4-9.2]	<0.001
Phosphorous (mmol/L)	3.3[2.8-3.9]	3.4[2.9-4.0]	3.3[2.7-4.0]	3.0[2.5-3.6]	<0.001

Magnesium (mmol/L)	2.2[2.0-2.5]	2.2[2.0-2.5]	2.1[1.9-2.4]	2.2[1.9-2.6]	<0.001
CRP (mg/L)	62.1[27.1-99.5]	56.0[19.8-98.3]	81.4[37.4-99.5]	49.5[28.8-111.8]	0.001
ESR (mm/h)	50.0[28.0-81.0]	44.0[26.0-75.0]**	56.0[36.0-87.0]	55.5[35.0-87.2]	<0.001
LDH (U/L)	603.5[472.7-793.0]	536.0[435.0-700.0]**	648.0[513.0-822.0]	713.5[532.5-925.0]	<0.001
hs-cTnI (pg/mL)	5.3[1.5-17.8]	6.0[1.5-19.8]	5.2[1.5-16.1]	4.4[1.5-16.4]	0.650
AST (U/L)	53.0[39.7-71.0]	50.0[38.0-67.7]	56.0[42.0-71.2]	55.5[41.0-76.7]	0.010
ALT (U/L)	39.0[29.0-56.0]	36.0[27.0-51.0]	43.0[31.0-61.2]	39.0[28.0-57.0]	<0.001
ALP (U/L)	175.0[137.0-232.0]	171.0[131.0-224.0]	175.5[142.7-237.0]	180.5[137.2-425.5]	0.108
In-hospital outcomes					
Hospital length of stay (day)	5.0[2.2-8.0]	4.0[2.0-7.0]**	6.0[3.0-9.0]	6.0[4.0-9.0]	<0.001
ICU admission	217(16.4%)	111(16.6%)	81(16.6%)	25(15.0%)	0.866
Severity	896(67.7%)	437(65.5%)	349(71.4%)	110(65.9%)	0.094
Mortality	235(17.8%)	114(17.1%)	91(18.6%)	30(18.0%)	0.798
ARDS	373(28.2%)	205(30.7%)	46(23.7%)**	52(31.1%)	0.022
Invasive ventilation	169(12.8%)	97(14.5%)	53(10.8%)	19(11.4%)	0.149
ACI	303(22.9%)	133(19.9%)	121(24.7%)	49(29.3%)	0.017
AKI	173(13.1%)	83(12.4%)	65(13.3%)	25(15.0%)	0.676
ALI	147(11.1%)	64(9.6%)	62(12.7%)	21(12.6%)	0.209
Multi-organ damage	260(19.7%)	127(19.0%)	95(19.4%)	38(22.8%)	0.551

Abbreviations: ACI: acute cardiac injury; AKI: acute kidney injury; ALI: acute liver injury; ALP: alkaline phosphatase; ALT: alanine transaminase; ARDS: acute respiratory distress syndrome; AST: aspartate aminotransferase; BMI: body mass index; BUN: blood urea nitrogen; CRP: C-reactive protein; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; hs-cTnI: high sensitive cardiac troponin I; ICU: intensive care unit; LDH: lactate dehydrogenase; LOC: loss of consciousness; SBP: systolic blood pressure; SII: systemic immune-inflammation index; WBC: white blood cells.

† Data are presented as mean±standard deviation, number (%), or median [interquartile range].

* Statistically significant *P*-values are bolded.

** Statistically significant post hoc Bonferroni's *P*-value (*P*-value<0.0083).

Figures

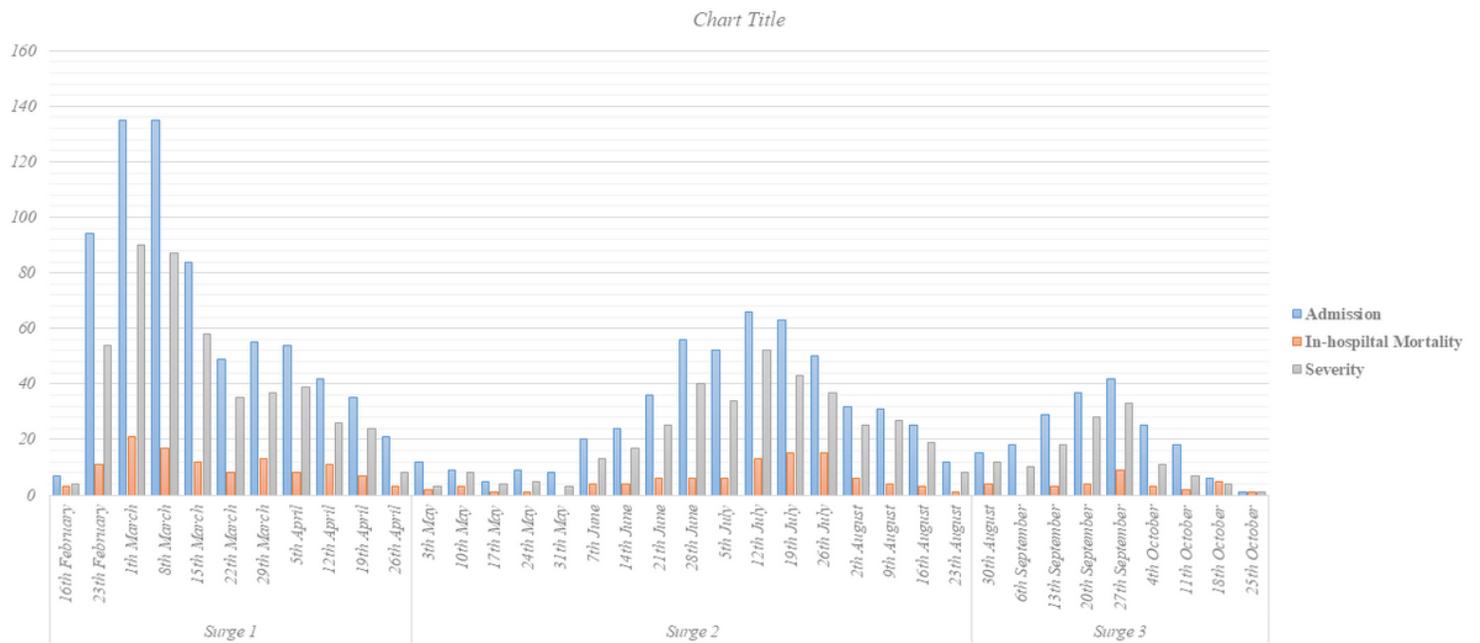


Figure 1

Census of patients admitted with coronavirus disease 2019 (COVID-19) with those who developed severe COVID-19 or were deceased across the first three surges of COVID-19 in Tehran, Iran.

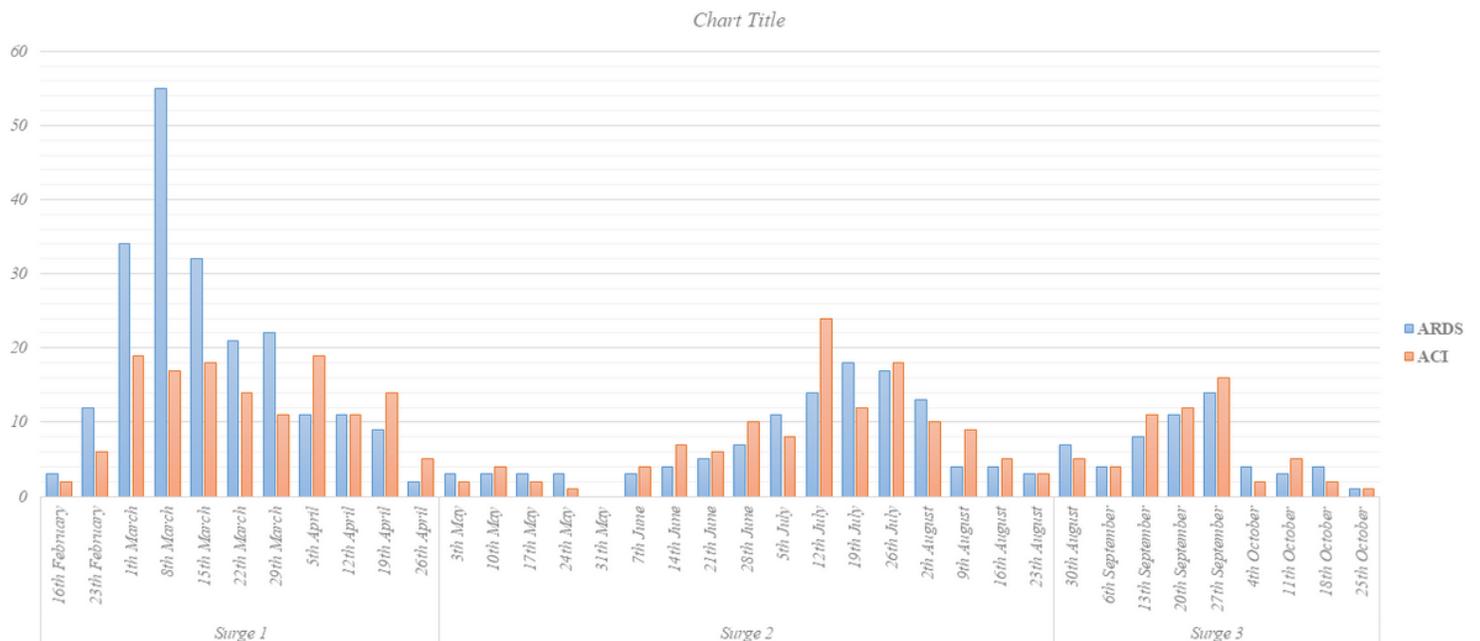


Figure 2

Number of patients who developed acute respiratory distress syndrome (ARDS) or acute cardiac injury (ACI) during the first three surges of coronavirus disease 2019 (COVID-19) in Tehran, Iran.