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Impact of comorbidities on mortality in hospitalized patients with COVID-19: An experience from Iran

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Abstract:

BACKGROUND: COVID-19 pandemic has spread all over the world. However, information regarding clinical characteristics and prognostic factors is scarce. The aim of this study was to explore the impact of preexistent chronic comorbid conditions and multimorbidity on risk of mortality in patients with COVID-19.

MATERIALS AND METHODS: We designed a retrospective, cross-sectional, observational, single-center study. Data were analyzed from all consecutive patients diagnosed with COVID-19 who admitted in a pandemic hospital affiliated with Tabriz University of Medical Sciences, Tabriz, Iran, from February 20, 2020, to September 25, 2020. The independent effects of preexistent conditions were evaluated using multivariate logistic regression model.

RESULTS: A total of 2597 hospitalized patients with COVID-19 were included. At least one preexistent condition was observed in 36.5% of study population. Multivariate logistic regression analysis showed that older age, male sex, diabetes, cardiovascular disease, hypertension, cancer, chronic kidney diseases, liver diseases, and chronic obstructive pulmonary disease were associated with increased risk of mortality. In addition, the number of comorbidities was significantly associated with increased odds of mortality compared to no-comorbidity.

CONCLUSION: The results of this study suggest that patients with comorbidities have an increased risk of in-hospital mortality following COVID-19 infection.

Keywords:

Comorbidity, Iran, mortality, multimorbidity, SARS-CoV-2

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Introduction

On March 11, 2020, the World Health Organization declared COVID-19 - which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – as a pandemic, after more than 110 thousand cases and more than 4000 deaths were reported in 114 countries.[1] As of February 2, 2020 (the date of preparing this manuscript), cases had reached over 109 million globally, with more than 2.4 million deaths attributed to this pandemic.[2] In addition to abovementioned toll, COVID-19 has burdensome effects on routine care for non-COVID-19 patients, resulting indirect morbidity and mortality burdens.[3,4]

Iran was one of the first countries after China to be affected by the pandemic.[5] After the first case of this infection was officially reported in Iran on February 2, 2020 in Qom province, it spread to every province in a few short days. As of November 7, 2020, there have been over 650,000 confirmed cases and around 37,500 fatalities.[5] However, official reports rely only on positive (reverse transcription-polymerase chain reaction [RT-PCR]) tests, raising the concern of under-reported cases and fatalities.[5]

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Iran has a different and more difficult position in its battle against COVID-19 pandemic. This public health crisis coincides with the ever-highest economic sanctions against the country,[6] affecting the Iranian healthcare system response.

One of the serious concerns of this pandemic is that healthcare systems may be overwhelmed beyond the capacity, especially regarding the provision of medical care to severe inpatient cases.[7] COVID-19–associated severe respiratory illness has been independently associated with risk of mortality, and increasing evidence substantiates the old ages and presence of chronic conditions in hospitalized patients with COVID-19.[8,9] In addition, multimorbidity is intimately linked to worse clinical outcomes,[10,11] which should be used in decision-making for clinical care.

To date, most studies regarding the COVID-19 and associated mortality were reported from developed countries.[12] For example, a study of more than 5000 patients who were infected with COVID-19 and were hospitalized in a large New York City health system showed that chronic conditions of hypertension, obesity, and diabetes were the most prevalent comorbidities; more than 14.0% of the inpatient COVID-19 population required care in the intensive care unit; 12.2% of them received invasive mechanical ventilation; and 21.0% of them died.[13] Despite the increasing number of cases and fatalities, there are limited data regarding clinical features and outcomes among Iranian patients admitted to pandemic hospitals. In addition, there is even more limited evidence describing the predictors of fatalities in their hospital course. A comprehensive understanding is essential to guide decision-makers regarding the effective management of admissions, hospital capacity, and therapeutic resources. We describe baseline characteristics of COVID-19 inpatients, coexistent clinical conditions, mortality, and the association of these characteristics with mortality.

Materials and Methods

Study design and setting

This was a retrospective observational cohort study, which was conducted from January to February 20, 2020, to September 25, 2020. The study setting was Imam Reza Hospital of Tabriz University of Medical Sciences. This Hospital, as a large tertiary care academic center that located in Tabriz, East Azerbaijan Province, was assigned responsibility for the treatment of patients with severe COVID-19 by health authorities.

Study participants and sampling

All consecutive patients admitted to the hospital with laboratory-confirmed COVID-19 were eligible in this study. Inpatient admission was according to the clinical judgment of treating emergency physicians. Laboratory and radiological examinations were conducted according to the treating physician's decision and national COVID-19–related guidelines.

To confirm COVID-19 infection, nucleic acids were extracted from clinical samples according to the kit instructions. The laboratory-based RT-PCR was applied as the main method to confirm COVID-19.

Data collection tool and technique

Data were obtained from the electronic health record system of the institution. Admission data included demographical characteristics of the patients such as age and gender, alongside with data regarding date of admission and date of discharge/death. Preexisting clinical conditions were ascertained through participant self-reports of doctor-diagnosed disease. The electronic medical record system retrieved data regarding whether the patient had a known diagnosis of hypertension, cardiovascular diseases (CVDs), diabetes mellitus, chronic kidney diseases (CKDs), liver diseases, chronic obstructive pulmonary disease (COPD), and cancer. We excluded patients who tested negative for COVID-19 or patients (even who tested positive for COVID-19) who not being hospitalized.

Descriptive statistics were estimated for all study variables. Continuous variables were compared for the study outcome using the *t*-test or the Mann–Whitney *U*-test, and categorical variables were compared conducting Chi-square tests or Fisher's exact tests, according to the distribution. Continuous data were reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) values. The finding was stratified by in-hospital survival status. Multivariate logistic regression was used to determine the impact of demographic characteristics, chronic conditions, and their co-occurrence, i.e., multimorbidity, on death during the hospitalization. Data were analyzed using Stata MP V.16 (StataCorp, College Station, TX).

Ethical consideration

The permission to conduct this study was given by the authorities of the Imam Reza Hospital. This study also approved by Research Ethics Committee of Islamic Azad University-North Tehran Branch.

Results

Figure 1 provides a flowchart of patient recruitment process. In total, 13,877 potential cases screened initially from February 20, 2020, to September 25, 2020. Finally, the study population included 2597 hospitalized patients with confirmed COVID-19.

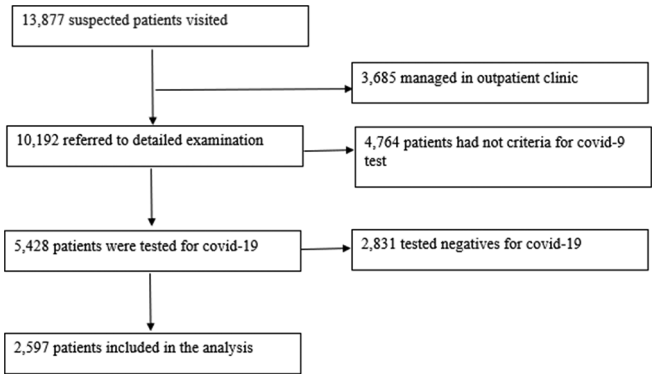

Figure 1: Study population recruitment process

The mean age was 62.1 years (SD = 16.8, median = 64, IQR = 50–75, range 11–100), and 1477 (56.8%) were male.

A total of 1019 patients (39.2%) had at least one preexistent comorbidity including hypertension (511 [19.6%]), diabetes (458 [17.6%]), CVD (233 [8.9%]), COPD (123 [4.7%]), CKD (79 [3.0%]), cancer (62 [2.4%]), and chronic liver diseases (27 [1.0%]). In terms of number of coexistent chronic conditions: 647 (24.9%) patients had one preexistent comorbidity, 279 (10.7%) had two comorbidities, and 93 (3.5.0%) reported three or more coexistent conditions [Table 1].

Overall, 718 patients (27.6%) died during their hospitalizations, 1739 (70%) were discharged alive from the hospital, and 140 (5.4%) remained hospitalized at the time of data analysis.

The multivariate logistic regression showed that older age (OR 2.25; 95% CI 1.87–2.71; $P < 0.001$) and male sex (OR 1.23; 95% CI 1.02–1.47; $P = 0.02$) are significantly associated with increased mortality. Among comorbidities, coexistent hypertension (OR 1.42; 95% CI 1.13–1.78; $P = 0.02$), diabetes (OR 1.58; 95% CI 1.25–1.99; $P < 0.001$), CVD (OR 1.40, 95% CI 1.04–1.88; $P = 0.02$), cancer (OR 3.19; 95% CI 1.87–5.45, $P < 0.001$), COPD (OR 1.46, 95% CI 0.99–2.17; $P = 0.05$), kidney (OR 1.70; 95% CI 1.06–2.75; $P = 0.02$), and liver diseases (OR 2.81; 95% CI 1.27–6.20) were significantly associated with mortality [Table 2].

In addition, we did a separate multivariate logistic regression to examine the effect of number of preexistent comorbidities on odds of in-hospital mortally among patients with COVID-19 infection. The results showed that the relationship between number of comorbidities and mortality is as follows (compared with $n = 0$ comorbidities): one comorbidity (OR 1.69; 95% CI 1.38–2.08), two comorbidities (OR 1.94, 95% CI 1.47–2.56), and three or more comorbidities (OR 4.92, 95% CI 3.17–7.65) ($P < 0.001$ for all).

Discussion

In a study of 2597 patients with laboratory-confirmed SARS-CoV-2 infection admitted to a pandemic hospital in Tabriz, Iran, we estimated a mortality rate of 27.6 deaths per 100 inpatient admission. This fatality rate among hospitalized patients varies substantially among the previous published reports worldwide. Overall, the estimated mortality rate for hospitalized COVID-19 patients is consistent with previously published reports, ranging between 14% and 28%.[14,15]

The observed difference in in-hospital case fatality rate can be explained by several factors such as different case mix and availability of healthcare services.[16] Specifically, older age, male sex, hypertension, liver disease, CKD, cancer, CVDs, COPD, and diabetes were significant risk factors for in-hospital mortality. These results are consistent with previously reported data that indicate preexistent comorbidities increase the likelihood of in-hospital mortality among patients infected with COVID-19.[17,18] For the effect of these chronic conditions, the mechanisms still remain unclear. These predictors can help healthcare providers and clinicians prognosticate outcomes and should be considered in treatment strategies.

In this retrospective single-center analysis, we observed a strong association of demographic and clinical characteristics with in-hospital mortality of COVID-19 patients. Older age was a significant risk factor for mortality as the mean age of fatalities was 68.3 years compared to 59.8 years for survivors. These results match those observed in earlier studies suggesting the vulnerability of the geriatric population in this pandemic.[19]

Although fatalities predominantly were occurred in the elderly population, one interesting finding from this study is that about 48% of hospitalized patients were younger than 64 years. In addition, we found that male gender was a significant predictor of death, supporting the findings of previous relevant works. This difference in gender vulnerability may explained by genetic, biological, and hormonal factors.[20,21] However, the results of this analysis have not reported a considerable male performance to COVID-19 hospitalization. However, the results of this analysis have not reported a considerable male performance to COVID-19 hospitalization.

In this study, preexistent morbidities are identified as significant risk factor for increased mortality from COVID-19 infection. This is in line with previous studies that identified the presence of common comorbidities as an important risk factor for increased

Table 1: Demographic, and clinical characteristics of patients on admission

Characteristics	Total (*n*=2597)	Survivor (*n*=1879)	Nonsurvivor (*n*=718)	*P*
Age (years), mean (SD)	62.1 (16.7)	59.8 (16.8)	68.3 (15.1)	<0.001
Age group (years), *n* (%)				
<64	1255 (48.3)	1017 (54.1)	238 (33.1)	<0.001
64+	1342 (51.7)	862 (45.9)	480 (66.9)	
Sex, *n* (%)				
Female	1120 (43.1)	829 (44.1)	291 (40.5)	0.05
Male	1477 (56.9)	1050 (55.9)	427 (59.5)	
Comorbidity, *n* (%)				
None	1578 (60.7)	1236 (65.7)	342 (47.6)	<0.001
CVD	233 (8.9)	138 (7.3)	95 (13.2)	<0.001
Hypertension	511 (19.6)	313 (16.6)	198 (27.5)	<0.001
Diabetes	458 (17.6)	275 (14.6)	183 (25.4)	<0.001
COPD	123 (4.7)	75 (3.9)	48 (6.6)	0.004
CKD	79 (3.0)	47 (2.5)	32 (4.4)	0.009
Cancer	62 (2.3)	31 (1.6)	31 (4.3)	<0.001
Liver diseases	27 (1.0)	13 (0.6)	14 (1.9)	0.005
Multimorbidity, *n* (%)				
None	1578 (60.8)	1236 (65.8)	342 (47.6)	<0.001
1 comorbidity	647 (24.9)	434 (23.1)	213 (29.7)	<0.001
2 comorbidities	279 (10.7)	172 (9.1)	107 (14.9)	<0.001
3+ comorbidities	93 (3.6)	37 (2.0)	56 (7.8)	<0.001

SD=Standard deviation, CVD=Cardiovascular diseases, COPD=Chronic obstructive pulmonary disease, CKD=Chronic kidney diseases

Table 2: Results of factors associated with mortality among hospitalized patients with confirmed coronavirus-2019 disease

Characteristics	OR* (95% CI)	*P*
Age (year)		
<64	1 (reference)	
≥64	2.25 (1.87-2.71)	<0.001
Gender		
Female	1 (reference)	
Male	1.23 (1.02-1.47)	0.02
Chronic conditions		
None	1 (reference)	
CVD	1.40 (1.04-1.88)	0.02
Hypertension	1.43 (1.14-1.79)	0.002
Diabetes	1.58 (1.25-1.99)	<0.001
COPD	1.46 (0.99-2.17)	0.05
CKD	1.70 (1.06-2.75)	0.02
Cancer	3.19 (1.87-5.45)	<0.001
Liver diseases	2.81 (1.27-6.20)	0.01
Multimorbidity		
None	1 (reference)	
1 comorbidity	1.69 (1.38-2.08)	<0.001
2 comorbidities	1.94 (1.47-2.56)	<0.001
3+ comorbidities	4.92 (3.17-7.65)	<0.001

95% CI=95% confidence interval, OR=Odds ratio, CVD=Cardiovascular diseases, COPD=Chronic obstructive pulmonary disease, CKD=Chronic kidney diseases

risk of COVID-19–related mortality.[22,23] In addition, the analysis showed that coexistence of comorbidities significantly increases the odds of mortality among hospitalized COVID-19 patients. This association becomes more intensive when number of comorbidities increases.[24]

The result of this study showed a high mortality rate among hospitalized patients with COVID-19. It is not yet clear whether the severity or level of management of underlying comorbid conditions affects the risk for worse outcomes associated with COVID-19. However, it is clearly essential that all persons should take steps to protect themselves from COVID-19 infection and to protect others. This is particularly important for those who are connected with persons with underlying conditions.

Limitation and recommendation

This study has several limitations that should be considered when interpreting the results. First, included patients are from a single academic hospital and factors that may be constitute the clinician's discretion regarding need to hospitalization of COVID-19 patients may differ across other geographical areas and health systems. This limitation challenges the comparability of the results. Second, chronic preexistent comorbidities in this study relied solely on self-report and medication history.[24]

In this circumstance, comorbidities may be underreported. In addition, in this study, only those variables that were available from the database of the study hospital were included in the analysis. Other potentially important information, such as results of clinical tests and examinations and other preexistent conditions, such as obesity were not part of this database. Moreover, for some preexistent clinical conditions and risk factors, such as cancer, few observations were included in the study; therefore, conclusions cannot be made regarding

the risk for COVID-19 mortality among patients in these groups. Finally, potential mortalities occurring outside of our hospital were not captured.

The optimal management strategy to care for critically-ill patients with COVID-19 in Iran is ongoing.[25] However, future research should seek to identify casual associations and to examine the relationship between different clinical interventions and patients' outcome. In addition, taking account of the severity of comorbid chronic conditions in investigating the association of comorbidities on in-hospital mortality of COVID-19 patients seems to be a necessity.

Conclusion

Overall, COVID-19 represents a huge challenge for healthcare system in the country. In this single-center study of hospitalized patients with COVID-19, 27.6% died during their hospitalization course. We identified patients' demographic characteristics and preexistent comorbid conditions that were associated with increased odds of in-hospital mortality.

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Conflicts of interest

There are no conflicts of interest.

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