Differences in the Clinical Severity Scores of Hospitalized COVID-19 Patients across Different Phases of an Epidemic Wave in Iran: a Secondary Analysis

Leila Mounesan[1,2], Safoora Gharibzadeh[2], Mahboubeh Parsaeian[3], Mohammad Mehdi Gouya[4], Sana Eybpoosh[1,2], Ali Hosseini[5], Leila Haghjou[6], AliAkbar Haghdoost[7], Ehsan Mostafavi[1,2]*

Abstract

Background: To reduce the clinical burden of COVID-19, healthcare providers, and policymakers need a clear understanding of the illness severity during epidemic waves. This study aimed to identify the clinical severity of patients with COVID-19 during different stages of an epidemic wave (pre-peak, peak, post-peak) in four provinces in Iran.

Methods: We conducted a secondary analysis of the data on COVID-19 patients admitted to hospitals (25,382 cases), which were recorded in the Medical Care Monitoring Center. Data included adult patients (≥18 years) who were hospitalized due to COVID-19 infection, confirmed by a positive SARS-CoV-2 RT-PCR test. No exclusion criteria were applied. A pairwise comparison method was used to evaluate clinical severity. Then, based on univariable and multivariable linear regression models, the severity scores of patients were compared during various stages of an epidemic wave.

Results: The findings showed that the level of severity of the disease was higher during and after the peak in the total population. The means (SD) of severity scores were 0.16 (0.25), 0.18 (0.26), and 0.19 (0.26) before, during and after the peak, respectively. Besides, age and the underlying disease had a positive and significant relationship with disease severity.

Conclusion: During the middle and late phases of the COVID-19 epidemic wave, hospitals are seeing patients with more severe illnesses than in the early stages. Enhancing hospital preparedness is essential to avert excess deaths and critical cases. Moreover, it is important to maintain ongoing monitoring of clinical symptoms during the recovery phase to support individual patients, guide public health policy, and enhance scientific understanding of epidemic recovery processes.

Keywords: COVID-19, Epidemics, Clinical Severity, Hospitalization

Introduction

Despite more than four years since COVID-19 broke out, epidemic waves can continue to spread due to its propagation nature. Epidemiological data from hospitals serve as a key source of disease monitoring and surveillance (1, 2).

Based on the literature, numerous studies have been conducted on the clinical characteristics or severity of hospitalized patients during the COVID-19 pandemic and have compared these characteristics in subsequent waves (3-5).

Corresponding author: Dr Ehsan Mostafavi, mostafavi@pasteur.ac.ir

1. Research Centre for Emerging and Re-emerging Infectious Diseases, Pasteur Institute of Iran, Tehran, Iran
2. Department of Epidemiology and Biostatistics, Pasteur Institute of Iran, Tehran, Iran
3. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
4. School of Medicine, Iran University of Medical Sciences, Tehran, Iran
5. Department of Human Geography, University of Tehran, Tehran, Iran
6. Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran
7. HIV/STI Surveillance Research Center and WHO Collaborating Centre for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

↑*What is "already known" in this topic:*
Healthcare providers and policymakers require a clear understanding of the COVID-19 severity during epidemic waves to reduce the clinical burden.

→*What this article adds:*
This study provides insights into the clinical severity of hospitalized COVID-19 patients across different stages of an epidemic wave (before, during, and after the peak), highlighting the significance of ongoing monitoring during the recovery phase to ensure timely interventions.

As the COVID-19 pandemic unfolds with multiple waves (6), there is a lack of evidence regarding whether the clinical severity of patients may vary during specific phases of an epidemic wave, particularly before, during, and after the peak time. Knowing a patient's clinical severity at various phases of an epidemic will help to better understand the current situation and formulate best practices for controlling infectious disease outbreaks (7-9).

The number of patients referred to medical centers or hospitalizations may change for different reasons, for instance, patient characteristics, changes in interventions, and policies like variations in the capacity of laboratory tests or therapeutic methods (10, 11). We can define two distinct situations for investigating epidemic phases: 1. Each wave consists of three phases pre-peak (p1), during the peak (p2), and post-peak (p3). 2. The intervals between epidemic waves are referred to as the bp phases. Typically, in the p2 phase, it is expected that the number of patients who require hospitalization and severe cases will increase. According to this, healthcare systems can be overwhelmed, leading to worse outcomes. During this phase, most efforts are focused on severe COVID-19 patients to save lives (12).

Moreover, sometimes people assume that the downward trend and passage of the peak signal the end of danger and the return to the normal situation, while each wave, depending on its magnitude, may have a long-term detrimental effect on one's health (13, 14).

In resource-constrained countries, where healthcare systems are more susceptible to pandemics (15), consistent monitoring of each wave is crucial for reducing the clinical burden of diseases. In this study, for the first time, we aimed to assess the clinical severity of COVID-19 hospitalized patients during different phases of the epidemic wave including pre-peak, peak, and post-peak in four provinces in Iran.

Methods

We conducted a secondary analysis of hospitalizations for laboratory-confirmed COVID-19 based on medical records in the "COVID-19 inpatient Dashboard" at the Medical Care Monitoring Center (MCMC), a national 24/7 center established to monitor healthcare service delivery. During the first nine months of the epidemic (from 19 February 2020 to 20 November 2020), four provinces, Mazandaran, Khuzestan, Kurdistan, and Khorasan Razavi, were selected from different geographical locations (north, south, west and east) using a convenience sampling strategy. These provinces were also considered in terms of their risk level for infection, using data gathered in late May and June 2020, when there were more investigations and diagnostic tests following the start of the epidemic in the country. Khuzestan and Kurdistan were identified as high-risk areas, while Razavi Khorasan and Mazandaran were considered lower risk at that time (16). The selected provinces are shown in Figure 1. During this period, the dominant strain of COVID-19 infection in the country was the Wuhan variant (Beta) and intervention measures including vaccination or specific drug treatments such as Remdesivir (one of the most widely used antiviral medications), were not available.

The recorded data included patient age of at least 18 years, admitted to the hospital for COVID-19, and SARS-CoV-2 genome positive by reverse transcription–-polymerase chain reaction (RT-PCR) test. All patients were included during the first 24 hours after hospitalization, and the disease symptoms were recorded based on the information obtained from them during this time. No exclusion criteria were applied.

First, 7-day moving average trends of hospitalized cases were plotted for each province. After conducting a visual normality check, the practical threshold for identifying three phases of an epidemic wave (p1, p2, and p3 phases) was set at the geometric mean plus one standard deviation. Regarding this, during the phase p2, the number of cases was equal to or larger than the threshold, and fewer cases were considered as phases before and after the peak (p1 starts from a plateau in the disease trend and ends when the number of cases reaches the peak threshold, while p3 starts from the peak threshold and ends when the number of cases reaches another plateau). The minimum time interval for each phase was at least 14 days (period of the diseases on

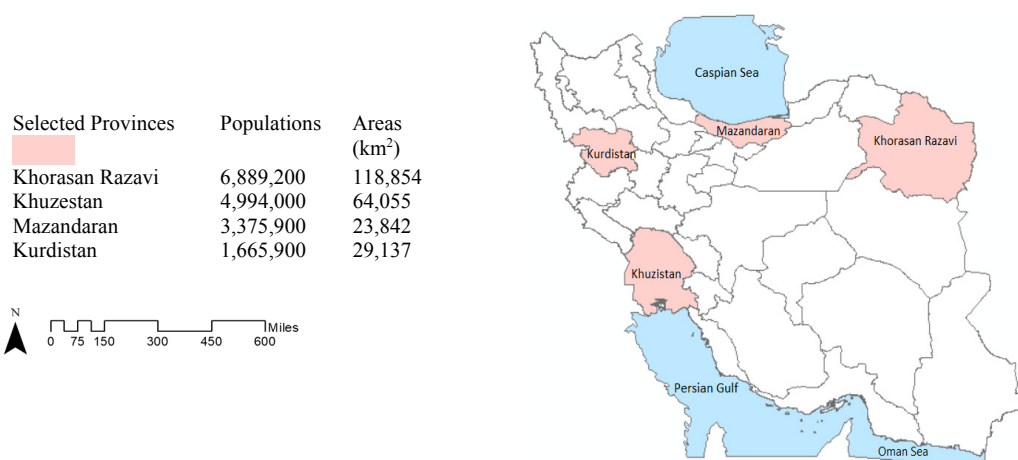| Selected Provinces	Populations	Areas (km^2)
Khorasan Razavi	6,889,200	118,854
Khuzestan	4,994,000	64,055
Mazandaran	3,375,900	23,842
Kurdistan	1,665,900	29,137

Figure 1. Geographical location map of selected provinces. Population size and area of provinces are shown on the left side (Map was created using ArcGIS 10.7 (ESRI, 2018)).

average). During 9 months, each province experienced two or three epidemic waves. From each province, the largest complete wave with three phases was selected for analysis.

Based on the literature (17-19) and the opinion of seven clinical experts, seven variables related to disease severity including respiratory distress, oxygen saturation (93% and less), deteriorated consciousness, hospitalization in an intensive care unit (ICU), intubation, referral status (the patient arrived by ambulance or not) and death, were selected. Then, variables were weighed using the Paired Comparison Method (20) and relative weight was assigned to each criterion based on their importance (scores were between 0.1 and 10). Finally, the disease severity score was calculated based on the total frequency of criteria by taking into account the specific weight of each criterion. The calculation of the Disease Severity Score is shown as follows:

Disease Severity Score = Σ (Frequency of Criterion i × Weight of Criterion i).

Where i represent each of the seven variables related to disease severity, and the weights are assigned based on their importance using the Paired Comparison Method.

Illness severity was compared in three phases in total and provincial levels by ANOVA and Chi-square tests. Furthermore, univariable linear regression models were used to investigate the relationship between disease severity and different wave phases. The multivariable linear regression model was performed to evaluate the severity of the disease in different phases of the epidemic wave, assuming the constant effect of other related variables (which had a *P*-value less than 0.2 in the univariable model).

Covariates: The underlying variables were age, sex, and history of at least one underlying disease (diabetes, immunodeficiency disorders, nervous system diseases, liver, renal and cardiovascular diseases). Common symptoms of the disease were fever, cough and muscle pain. Since the variable 'duration of hospitalization' is likely influenced by both the exposure variables and the outcome (disease severity) and is considered a 'collider' variable, it was not included in the modeling process.

Model selection: The stepwise backward Wald method with a lock term of epidemic phases was used to refine the regression model. This method is particularly useful for selecting the most relevant variables and enhancing the model's predictive accuracy.

Analyses were performed using STATA 14 software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.), and the P-value less than 5% was considered statistically significant.

Results

The data of 25382 hospitalized patients with COVID-19 from Khorasan Razavi (7741 people), Khuzestan (10285 people), Kurdistan (1598 people), and Mazandaran (5758 people) were analyzed. Characteristics of hospitalized COVID-19 patients in the largest epidemic wave in four provinces are shown in Table 1.

The mean and standard deviation of disease severity scores before (p1), during (p2), and after (p3) the peak in four provinces were as follows: Khorasan Razavi province 0.22 (0.28), 0.23 (0.27), and 0.20 (0.25); Khuzestan province 0.13 (0.23), 0.19 (0.27), and 0.24 (0.30); Kurdistan province 0.13 (0.21), 0.20 (0.25), and 0.18 (0.22); Mazandaran province 0.08 (0.17), 0.12 (0.21), and 0.12 (0.21). Additionally, the mean scores of the total target population in the four provinces in three periods (p1, o2, and p3) were 0.16 (0.25), 0.18 (0.26), and 0.19 (0.26), respectively.

Among hospitalized patients in four provinces, the proportion of deaths, ICU admissions, decreased oxygen levels, and respiratory distress in phases p2 and p3 was significantly higher than in phase p1 (*P* < 0.001) (Table 2).

Table 1. The background characteristics of confirmed COVID-19 hospitalized patients in the largest epidemic wave in four provinces

Variable	Khorasan Razavi	Khuzestan	Kurdistan	Mazandaran	Total population
Age Mean (SD)	58.9 (20.01)	55.06 (18.17)	56.60 (18.80)	54.91 (17.67)	56.04 (18.73)
Sex Frequency (%)	4059 (52.44)	5500 (53.48)	794 (49.69)	2702 (46.93)	13055 (51.43)
Underlying Disease Frequency (%)	2449 (31.64)	2517 (24.47)	353 (22.09)	2037 (35.38)	7356 (28.98)
Duration of Hospitalization Median (IQR)	5 (3-9)	5 (2-8)	4 (2-7)	6 (4-8)	5 (3-8)

Table 2. The variables related to the severe disease in different phases of epidemic waves in four provinces

Characteristics	Epidemic phases	Khorasan Razavi	*P*	Khuzestan	*P*	Kurdistan	*P*	Mazand aran	*P*	Total population
Death No. (%)			<0.001		<0.001		0.012		<0.001	
	Before the peak	245 (22.58)		146 (14.11)		58 (14.79)		24 (8.42)		473 (16.91)
	During the peak	1582 (27.11)		1904 (22.11)		220 (21.86)		646 (12.70)		4352 (21.19)
	After the peak	185 (22.50)		173 (27.03)		39 (19.50)		44 (11.28)		441 (2149)
Hospitalization in ICU / CCU No. (%)			0.031		<0.001		0.064		0.737	
	Before the peak	151 (13.91)		119 (11.50)		31 (7.90)		34 (11.92)		335 (11.98)
	During the peak	935 (16.02)		1227 (14.24)		123 (12.22)		684 (13.45)		2969 (14.45)
	After the peak	151 (18.36)		180 (28.12)		24 (12.00)		54 (13.84)		409 (19.93)

Table 2. Continued

Characteristics	Epidemic phases	Khorasan Razavi	P	Khuzestan	P	Kurdistan	P	Mazand aran	P	Total population
	Before the peak	151 (13.91)		119 (11.50)		31 (7.90)		34 (11.92)		335 (11.98)
	During the peak	935 (16.02)		1227 (14.24)		123 (12.22)		684 (13.45)		2969 (14.45)
	After the peak	151 (18.36)		180 (28.12)		24 (12.00)		54 (13.84)		409 (19.93)
Intubation No. (%)			<0.001		0.027		0.024		<0.001	
	Before the peak	152 (14.00)		97 (9.38)		18 (4.59)		12 (4.21)		279 (9.97)
	During the peak	595 (10.19)		985 (11.43)		87 (8.64)		236 (4.64)		1903 (9.26)
	After the peak	63 (7.66)		87 (13.59)		12 (6.00)		35 (8.97)		197 (9.60)
Loss of consciousness No. (%)			<0.001		<0.001		0.034		0.095	
	Before the peak	126 (11.61)		20 (1.93)		8 (2.04)		3 (1.05)		157 (5.61)
	During the peak	482 (8.26)		449 (5.21)		43 (4.27)		149 (2.93)		1123 (5.46)
	After the peak	68 (8.27)		68 (10.62)		3 (1.50)		15 (3.82)		154 (7.50)
Oxygen saturation (<93%) No. (%)			<0.001		0.015		<0.001		<0.001	
	Before the peak	629 (57.97)		287 (27.75)		174 (44.38)		38 (13.33)		1128 (40.34)
	During the peak	3976 (68.15)		2752 (31.95)		727 (72.26)		1290 (25.37)		8745 (42.58)
	After the peak	520 (63.26)		213 (33.28)		148 (74.00)		105 (26.92)		986 (48.05)
Respiratory Distress No. (%)			<0.001		<0.001		<0.001		<0.001	
	Before the peak	675 (62.21)		339 (32.78)		166 (42.34)		86 (30.17)		1266 (45.27)
	During the peak	4029 (69.06)		4650 (54.00)		635 (63.12)		2297 (45.18)		11611 (56.54)
	After the peak	511 (62.16)		358 (55.93)		121 (60.50)		152 (38.97)		1142 (55.65)
Use of ambulance service No. (%)			0.072		<0.001		0.062		<0.001	
	Before the peak	323 (29.76)		228 (22.05)		23 (5.86)		21 (7.36)		595 (21.28)
	During the peak	1685 (28.88)		1321 (15.34)		138 (13.71)		310 (6.09)		3454 (16.82)
	After the peak	246 (29.92)		135 (21.09)		16 (8.00)		35 (8.97)		432 (21.05)

The most important criteria associated with COVID-19 severity in the weighting process were death (0.44), intubation (0.15), ICU admission (0.14), deteriorated consciousness (0.12), low oxygen saturation (0.05), respiratory distress (0.05) and referral status (0.02), respectively.

Both univariable and multivariable linear regressions indicated that the frequency of illness severity was higher during phases p2 and p3 in the four provinces when comparing different phases of the epidemic wave. In the univariable model, the assessments of the COVID-19 severity in three phases at provincial levels revealed that in Khuzestan, Kurdistan, and Mazandaran, the severity of the disease was higher during p2 and p3, but in the Khorasan Razavi, although this average was higher during the p2 phase, it was not statistically significant (Table 3).

Furthermore, in the multivariable model, age and history of underlying disease had a significant positive relationship with disease severity ($P < 0.001$), and this relationship with the cough as a general symptom of the disease was significantly negative ($P < 0.001$) (Table 4).

Discussion

We investigated the illness severity in hospitalized COVID-19 patients in four provinces to explore the question of whether these characteristics differ during different phases of an epidemic wave.

The univariable and multivariable regression models showed that the COVID-19 severity index increased during phases p2 and p3 among all patients. At the provincial level, COVID-19 severity was higher during p2 and p3 in three provinces. Targeted health planning, considering local situations, could make the current system more effective, equitable, and accessible to the population.

Variations of clinical features during a wave's time intervals may be influenced by various factors, including demographic data, disease transmission, patient referral patterns, local legislation, and service delivery. As expected, the patients with worse health conditions are more likely to be hospitalized during the p2 due to the high load and burden of the disease, as well as the higher proportion of critically ill patients. On the other hand, there are some hypotheses on the severity of the disease after the peak, including the high burden of the disease during the peak, delay in severe consequences of illness like death and hospitalization in the ICU, more cases of long-term COVID-19 and the underestimation of disease risk by people in the phase p3 (10, 21). All mentioned factors can affect the recovery rates after the peak. Besides, disease severity and mortality rate indifferent phases can be in terms of changes in the patient characteristics such as age and history of underlying diseases. Demographic changes in the Iranian population, which are ageing the country, could create more pressure on disease management during emergencies and pandemics (22). In a study in Israel, the results showed that COVID-19 mortality

Table 3. Univariable linear regression model comparing severe disease in different phases of epidemic waves in four provinces

Disease severity core/population	Variable*	Coef.	t statistics	P>|t| (Univariable model)
Khorasan Razavi				
	During the peak	0.01	1.48	0.140
	After the peak	-0.02	-1.60	0.109
Khuzestan				
	During the peak	0.06	6.44	<0.001
	After the peak	0.11	8.15	<0.001
Kurdistan				
	During the peak	0.07	5.05	<0.001
	After the peak	0.05	2.52	0.011
Mazandaran				
	During the peak	0.04	2.94	0.003
	After the peak	0.04	2.30	0.020
Total population				
	During the peak	0.02	4.70	<0.001
	After the peak	0.03	4.76	<0.001

*"Before the peak" is the reference category.

Table 4. Multivariable and univariate linear regression model comparing severe disease status in the total population

Disease severity score/total population	Variable*	Coef.	t statistics	CI	P>|t| (Multivariable models)	P>|t| (Univariable model)
	During the peak	0.01	4.36	0.006, 0.02	<0.001	<0.001
	After the peak	0.01	3.00	0.004, 0.02	0.003	<0.001
Total population	Age	0.0007	15.96	0.0006, 0.0008	<0.001	<0.001
	Underlying diseases	0.02	9.68	0.01, 0.02	<0.001	<0.001
	Cough	-0.005	-3.54	-0.009, - 0.003	<0.001	<0.001

*"Before the peak" is the reference category.

rates were significantly associated with heavy patient load (23).

In the current study, although the clinical severity scores of COVID-19 have slightly increased during the phases, and the differences were minimal, serious complications such as death are still important even in small numbers. Additionally, no evidence was found regarding the Minimum Clinically Important Difference (MCID) criterion for COVID-19- patients in the literature (24).

Therefore, strengthening preparedness through the targeted interventions, i.e., allocating sufficient resources to the clinical sector, and improving access to medicines, vaccines, and health products is required during the phases p2 and p3 to prevent excess mortality and serious illness (12, 25).

The findings of this study also represented that severe diseases had a positive and significant relationship with variables, such as age and history of the underlying disease. These results are consistent with findings from other studies (17, 18, 26). Some hypotheses suggest that a decrease in mortality may be due to a reduced hospital load and improved handling of difficult illnesses by healthcare teams over time (27).

Clinical information on a large population of hospitalized patients during different phases of an epidemic wave can give us a comprehensive view of the overall variations in clinical severity on a national scale. However, various aspects, such as the characteristics of the target population, health infrastructures, and policy interventions, should be considered when interpreting the results.

Conclusion

In conclusion, hospitals in the middle and end of the epidemic wave are facing patients with more severe diseases than in the initial phase of the disease. Particularly, a higher proportion of severe COVID-19 cases in phase p3 is a cause for concern, as it can be attributed to factors such as limited hospital resources and delayed referral of patients for hospitalization. To prevent excess COVID-19 mortality and critical conditions, it is necessary to enhance the readiness of the hospitals until the end of the peak. In addition, to prepare the medical system in times of crisis, health policymakers need to take the necessary precautions to declare the end of the state of emergency and exit the epidemic phase.

his valuable comments on data interpretation.

Conflict of Interests

Dr MMG had been the former director of the Iranian Center for Communicable Diseases at Ministry of Health during the time of the study. All other authors declare that they have no competing interests. All other authors declare that they have no competing interests.

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