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Association Between rRT-PCR Test Results Upon Admission and Outcome in Hospitalized Chest CT-Positive COVID-19 Patients: A Provincial Retrospective Cohort with Active Follow-up

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic imposed the most devastating challenge on healthcare systems worldwide. Iran was among the first countries that had to confront serious shortages in reverse-transcriptase-polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) and ventilators availabilities throughout the COVID-19 outbreak.
Objectives: This study aimed to investigate the clinical course of hospitalized COVID-19 patients with different real-time RT-PCR test results during the first three weeks of the outbreak in Qazvin province, Iran.
Methods: In this retrospective cohort study, patients with a positive chest computed tomography (CT) scan for COVID-19 who were admitted to all 12 hospitals across Qazvin province, Iran, between February 20 and March 11, 2020, were included and followed up until March 27, 2020. A multivariate logistic regression model was applied to compare the independent associates of death among COVID-19 patients. Then, patients were categorized into six groups based on admission to the intensive care unit (ICU) and rRT-PCR test status (positive, negative, or no test). Also, multilevel logistic regression was used to compare the odds of surviving in each group against the reference group (PCR negative patients not-received ICU) to show if the rational allocation of ICU occurred while its capacity is limited.
Results: In this study, we included 998 patients (57% male; median age: 54 years) with positive chest CT scan changes. Among them, 558 patients were examined with rRT-PCR test and 73.8% tested positive. Case fatality rate (CFR) was 20.68 and 7.53% among hospitalized patients with positive and negative tests, respectively. While only 5.2% of patients were admitted to the ICU, CFR outside ICU was 17.70 and 4.65% in patients with positive and negative results not admitted to the ICU, respectively.
Conclusions: Total CFR in all hospitalized COVID-19 patients in Qazvin province during the first three weeks of the pandemic was 11.7%. Also, according to the results, the main risk factors included a positive rRT-PCR test, age more than 70 years, and having two or more comorbidities or just immunodeficiency disorders. Hence, the ICU admission criteria or prioritized ICU beds allocation should be considered with more emphasis on rRT-PCR results when the capacity of ICU beds is low.

Keywords: COVID-19, rRT-PCR, Pandemic, Cohort Study

1. Background

The first report of coronavirus disease 2019 (COVID-19) in Iran was officially announced on February 19, 2020, from the city of Qom in central Iran (1). Shortly thereafter, cases of infection with the novel coronavirus were reported from all over the country.

Although case fatality rate (CFR) in patients admitted to hospital and its associated clinical factors are some of the most substantial indicators that should be evaluated in COVID-19 pandemic, the complexity, and challenges, particularly in initial weeks of the pandemic, can cause lots of uncertainty. Among these complexities are: The rate of hospital and intensive care unit (ICU) admission (the former as the denominator of the CFR and the latter as one of the main courses of treatment), the criteria for hospital and ICU admissions, sensitivity and specificity of the diagnostic tests (including real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) and computed tomography (CT scan), low access to and experience with diagnostic tests, and last but not least the treatment regimens administered. Furthermore, such factors as changing the definitions and criteria, inadequate hospital dataset standards, and incomplete data can dramatically change CFR assessment.

In the first wave of COVID-19 outbreak, when debates on the effect of anti-viral or any other drug regimen are still challenging, effective ICU services for the management of severe cases is crucial, although deficiencies may occur due to the number of cases or inappropriate allocation protocols. This situation provided a unique opportunity to not only assess the clinical pattern and outcome of the disease in Qazvin province, Iran but also, evaluate the performance of 12 hospitals throughout the province during the critical first three weeks of emergence the outbreak.

The results of such an assessment can further be employed as a basis for more precise hospital and ICU admission criteria aimed at saving more lives in the subsequent critical phases of the epidemic.

2. Objectives

Little data has been documented about the course and outcome of the affected patients in the country since the emergence of the COVID-19 epidemic in Iran. In this retrospective cohort study, we aimed to investigate the clinical pattern and outcome of patients with a primary diagnosis of COVID-19 but different rRT-PCR test results admitted to the hospitals and ICUs of Qazvin province Iran, from February 20, 2020, to March 11, 2020.

3. Methods

In this retrospective cohort study, patients with a primary diagnosis of COVID-19 (see definition) admitted to all 12 hospitals across Qazvin province, Iran, from February 20, 2020, to March 11, 2020, were included and followed up until March 27, 2020.

Upon the outbreak, the Qazvin University of Medical Sciences, as the provincial health governing body, provided an electronic data entry platform to collect epidemiologic and clinical data related to patients with COVID-19 and mandated all involved hospitals within the province to employ the database. Data were collected from patients' medical records and entered into the electronic database during the patients' admission period. This acquisition of data included epidemiological and clinical data, patients' exposure history, as well as the results of their COVID-19 rRT-PCR test and clinical outcome (i.e., discharge or death). After the discharge of patients, they were followed up by phone until March 27, 2020 to confirm the outcome.

This study was approved by the Research Ethics Committee of Qazvin University of Medical Sciences (Code: IR.QUMS.REC.1399.007). An informed consent was obtained from the patients upon admission.

3.1. Inclusion Criteria

Patients were admitted with a primary diagnosis of COVID-19 based on the INIGCDT (2). This edition, published on February 24, 2020, limited the indications for rRT-PCR testing to detect SARS-CoV-2 to those admitted with severe respiratory signs and symptoms or admitted patients with fever whose chest imaging revealed pulmonary infiltration (3). According to the guidelines of the INIGCDT, a primary diagnosis of COVID-19 is characterized by symptoms of fever, cough, or myalgia (referred herein as minor clinical criteria), coupled with either A) respiratory distress, low pulse oximetry reading (SpO2 $\leq$ 93%), respiratory rate (RR) of $>$ 30 (herein considered as major clinical criteria), or decreased level of consciousness; or B) patients being among high-risk groups who have an underlying medical condition along with suggestive chest X-ray or CT scan changes for COVID-19 (see below). Further laboratory and chest imaging studies were performed during the patients' admission course.

A definitive diagnosis of COVID-19 was made using rRT-PCR to detect SARS-CoV-2 in patients' respiratory secretions. The test became available through the Pasteur Institute of Iran in early February 2020. Throat swab (nasopharyngeal and oropharyngeal) for initial diagnosis and lower respiratory secretion specimens (by induced sputum sample or in intubated patients) for definitive diagnosis were obtained from patients and sent for SARS-CoV-2 PCR test during their admission course. However, due to a serious shortage of these tests in Iran at the time, patients were not reexamined.

Fever was defined as an oral temperature of $>$ 37.8°C. Shortness of breath and decreased level of consciousness were defined upon the triage physician's clinical judgement. Underlying medical conditions that justified patients' admission, as proposed in the INIGCDT, included a history of cardiovascular disease, pulmonary disease, diabetes, hypertension, cancer, human immunodeficiency virus (HIV) infection, and organ transplantation. Chest X-ray or CT scan changes suggestive of COVID-19 consisted of bilateral patchy infiltration with rapid progression toward ground glass opacity (GGO) (2, 3).

Patients were admitted to ICUs if they had persistent hypoxemia, decreased level of consciousness, hemodynamic instability, or hypercapnia.

Patients were discharged from the hospital if they had no fever for more than 48 - 72 hours, had an SpO2 of > 93% while breathing ambient air, had improved clinical symptoms and signs, and showed remarkable improvement in their serial chest imaging.

For comparison, patients were categorized into four groups including: (1) survivors outside the ICU; (2) survivors inside the ICU; (3) non-survivors outside the ICU; and (4) non-survivors inside the ICU.

3.2. Patients' Follow-up

The patients who were admitted during the third week of the study period (5 - 7 March, 2020) were actively followed up using phone interviews on March 27. Among them, 436 patients (response rate = 76.7%) were reached.

3.3. Statistical Analysis

Descriptive analyses were carried out using the median (IQR). Patients were categorized based on their week of admission, outcome inside and outside the ICU, and their rRT-PCR testing status. The CFR was assessed for each group. The chi-square test was employed to assess differences in study variables among the different categories of patients.

A multiple logistic regression model was applied to identify the factors associated with death in COVID-19 patients. The odds ratio (OR) and 95% confidence interval (CI) were determined for each contributing factor. Then, patients were categorized into six groups based on receiving the intensive care services and rRT-PCR test status (positive, negative, or no test). Also, multilevel logistic regression was used to compare the odds of surviving in each group against the reference group (PCR negative patients not-received ICU) to show if the rational allocation of ICU occurred while its capacity is limited. The constructed model was adjusted for sex, age, Charlson Comorbidity Index (CCI), calendar time, oxygen saturation, and type of hospital. The difference between compared groups was summarized in terms of OR. It also allowed us to calculate the mortality rate for each PCR/ICU group adjusted for factors associated with in-hospital mortality using the 'margins' and 'predict' commands in Stata software version 14.1.

Statistical analysis was performed using the Stata statistical software package (StataCorp. 2014. Stata Statistical Software: Release 14.1, College Station, TX: StataCorp LP). A P value < 0.05 was considered as significant.

4. Results

The data of 1,197 patients admitted to hospitals in Qazvin province were entered into the related electronic database from February 20 to March 11, 2020. Among these patients, 191 patients who were PCR-negative and were admitted to non-COVID-19 wards were excluded from the analysis; however, their clinical course was followed up, as with all patients. The CFR among the latter group was 3.1%, with none of them being admitted to ICUs. Furthermore, eight patients whose death occurred within the first 24 hours of their admission were excluded from the study (Figure 1).

A total of 998 patients (57% male) with a median age of 54 (IQR 25 - 75 = 25) years were analyzed. Among them, 558 patients were tested for COVID-19, with 412 testing positive and 146 testing negative. ICU care was provided for 52% of patients, while the remaining 48% were isolated in the designated wards where they received low-flow oxygen and medical therapy (Table 1).

Comparing the study participants' characteristics between the four groups of survivors and non-survivors outside and inside the ICU, no sex difference in CFR was found (P = 0.674). Among the non-survivors, except for those aged < 50 years, death rates were higher in patients outside the ICU than inside; this difference was more prominent among patients aged > 70 years (23.04 vs. 4.15%, respectively). Notably, in the rRT-PCR test-positive group, a 20.68% CFR was observed (Table 2).

Comparing the study participants based on their PCR test results, it was found that while most tests had been carried out on individuals aged > 70 years than the younger age groups, there was no statistically significant age difference between positive and negative rRT-PCR patients. Moreover, although patients receiving ICU services were tested more than non-ICU admitted patients, positive results were more prevalent in the latter group (Table 3).

The CFR among admitted patients in Qazvin province was 11.7% (Table 1); however, the CFR differed between the various groups (Table 4). A multiple logistic regression model including age group, sex, type of hospital (i.e., teaching or non-teaching; high volume or low volume), week of admission, ICU admission, co-existing disorders, and rRT-PCR test results was used to determine the factors associated with death in patients. The results showed that age > 70 years (OR = 5.2; 95% CI = 2.9 - 9.1; P $\leq$ 0.001), immunodeficiency disorders (OR = 4.3 ; 95% CI = 1.11 - 17.23; P = 0.035), ICU admission (OR = 11.5; 95% CI = 5.5 - 23.9; P $\leq$ 0.001), and having positive rRT-PCR test results (OR = 5.8; 95% CI = 2.7 - 12.5; P $\leq$ 0.001) were the main determinants of death in patients. Also, having two comorbidities or more was a weak risk factor for death (OR = 1.8 ; 95% CI = 0.92 - 3.06;

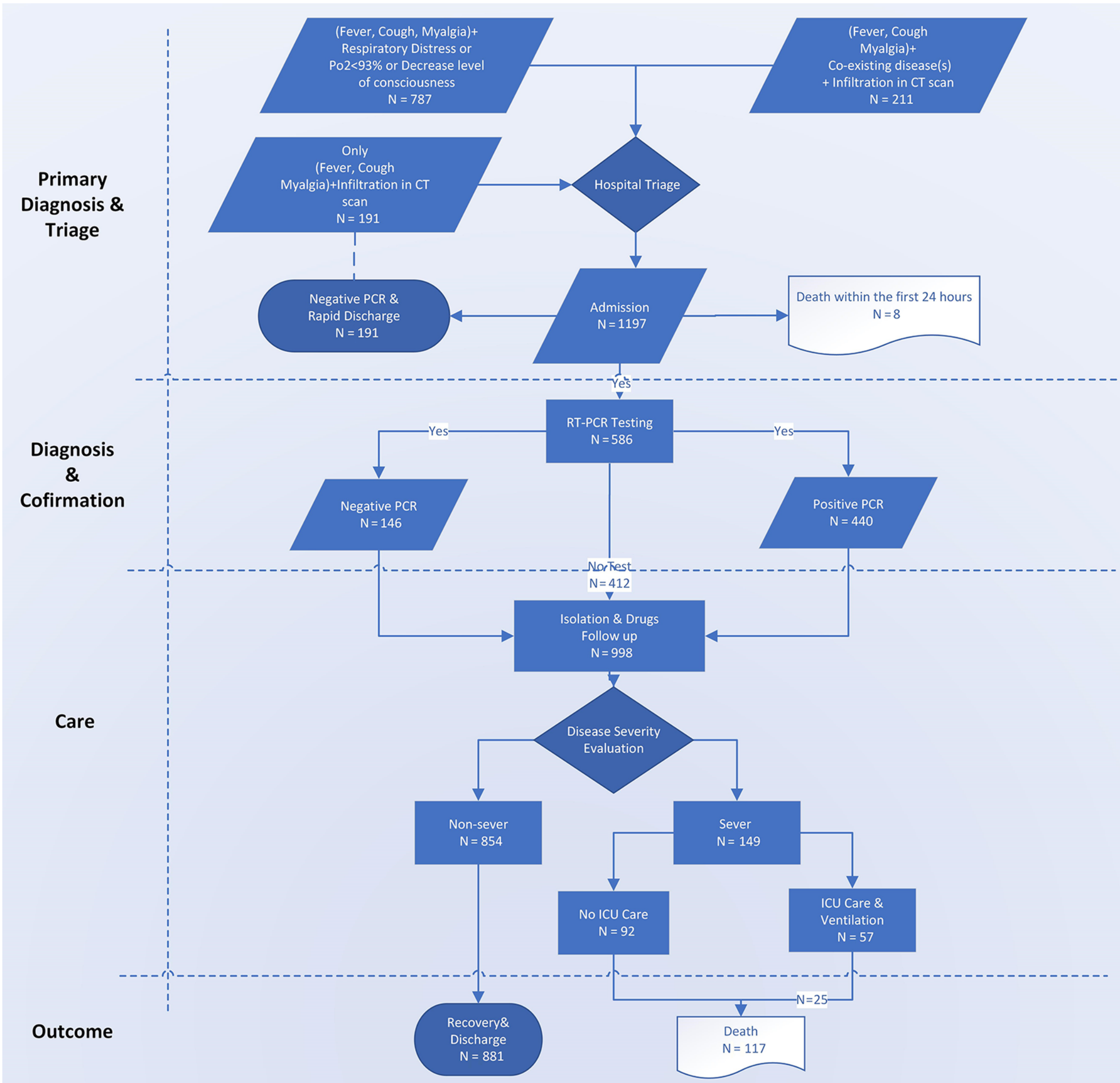

Figure 1. The patients' flow diagram

P = 0.08). After multi-level regression analysis in the six above-mentioned groups, only the two groups with positive rRT-PCR test results showed significantly higher mortality rates in comparison to the reference group after controlling the effects of confounding variables (OR = 16.8; 95% CI = 5.6 - 49.7; P < 0.001 in ICU admitted group and OR = 4.0; 95% CI = 1.8 - 8.9; P = 0.001 in the non-ICU admitted group).

5. Discussion

The present study was conducted in the first critical three weeks of the novel coronavirus outbreak in Qazvin province, Iran. The results showed that while CFR was 7.5% among CT-diagnosed COVID-19 patients with typical respiratory symptoms but negative rRT-PCR results, this rate was as high as 20.7% in test-positive patients.

As shown in Table 1, a similar CFR was observed in both males and females. This finding is in line with the reports from Wuhan, China (3). On the other hand, the CFR in pa-

Table 1. Basic Characteristics of the Study Participants [a]

Variables	Week 1 (N = 116)	Week 2 (N = 399)	Week 3 (N = 483)	Total (N = 998)
Sex				
Female	57 (49.14)	168 (42.11)	204 (42.24)	429 (42.99)
Male	59 (50.86)	231 (57.89)	279 (57.76)	569 (57.01)
Age group (y)				
< 50	55 (47.41)	167 (41.85)	180 (37.27)	420 (40.28)
51 - 60	21 (18.10)	86 (21.55)	85 (17.60)	192 (19.24)
61 - 70	17 (14.66)	74 (18.55)	96 (19.88)	187 (18.74)
$\geq$ 70	23 (19.83)	72 (18.05)	122 (25.26)	217 (21.74)
Admission criteria				
Minor clinical criteria [b] plus at least one major criteria [c]	92 (79.31)	317 (79.45)	378 (78.26)	787 (78.86)
Co-existing disorders OR immunodeficiency [d]	24 (20.69)	82 (20.55)	105 (21.74)	211 (21.14)
rRT-PCR test status				
Positive	33 (28.45)	200 (50.13)	207 (42.86)	440 (44.09)
Negative	20 (17.24)	49 (12.28)	77 (15.94)	146 (14.63)
Not tested	63 (54.31)	150 (37.59)	199 (41.20)	412 (41.28)
ICU admission				
No	108 (93.10)	377 (94.49)	461 (95.45)	946 (94.70)
Yes	8 (6.90)	22 (5.51)	22 (4.55)	52 (5.21)
Co-existing disorders				
Two or more comorbidities	12 (12.12)	32 (9.94)	36 (9.00)	80 (9.74)
Cardiovascular diseases	16 (13.79)	41 (10.28)	53 (10.97)	110 (11.02)
Diabetes	13 (11.21)	43 (10.78)	49 (10.14)	105 (10.52)
Hypertension	4 (3.45)	30 (7.52)	23 (4.76)	57 (5.71)
Chronic pulmonary diseases	4 (3.45)	17 (4.26)	9 (1.86)	30 (3.01)
Immunodeficiency [d]	1 (0.86)	6 (1.50)	9 (1.86)	16 (1.60)
Chronic renal diseases	1 (0.86)	4 (1.00)	5 (1.04)	10 (1.00)
Total	30 (25.86)	111 (27.82)	124 (25.67)	265 (26.55)
Hospital type				
Teaching	92 (79.31)	317 (79.45)	360 (74.53)	769 (77.05)
High volume non-teaching	17 (14.66)	78 (19.55)	117 (24.22)	212 (21.24)
Low volume [e] non-teaching	7 (6.03)	4 (1.00)	6 (1.24)	17 (1.70)
Outcome				
Recovery	104 (89.66)	352 (88.22)	425 (87.99)	881 (88.28)
Death	12 (10.34)	47 (11.78)	58 (12.01)	117 (11.72)

[a] Values are expressed as a proportion (%) of the total number of patients for each week, as well as the total.
[b] Minor clinical criteria: Fever, cough, and myalgia.
[c] Major clinical criteria: Low SpO2, shortness of breath, unconsciousness.
[d] Immunodeficiency includes HIV infection and AIDS, cancer, immunodeficiency disorders, and receiving chemotherapy.
[e] Low volume hospitals indicate hospitals with less than 20 admitted COVID-19 patients.

tients aged > 70 years and in those who were ICU-admitted was higher compared to the reference group. Nevertheless, we did not find a significant increased death rate among COVID-19 patients with coexisting diseases. The exception, however, was in those with immunodeficiency disorders, in whom the CFR was about four times that of

Table 2. Comparison of Different Prognostic Factors Between Survivors and Non-survivors in ICU-Admitted and Non-ICU Admitted Patients [a, b, c, d, e, f]

Variables	Total (N = 998)	Non-survivors; N = 117 (11.7%)		Survivors; N = 881 (88.3%)		P Value
		Outside ICU (N = 92)	Inside ICU (N = 25)	Outside ICU (N = 854	Inside ICU (N = 27)	
Sex						
Female	429 (42.99)	40 (9.32)	8 (1.87)	368 (85.78)	13 (3.03)	
Male	569 (57.01)	52 (9.14)	17 (2.99)	486 (85.41)	14 (2.46)	0.674
Age group (y)						
< 50	402 (40.28)	17 (4.05)	7 (6.67)	372 (88.57)	6 (1.43)	
51 - 60	192 (19.24)	9 (4.69)	3 (1.56)	174 (90.63)	6 (3.13)	
61 - 70	187 (18.74)	16 (8.56)	6 (3.21)	160 (85.56)	5 (2.67)	
≥ 70	217 (21.74)	50 (23.04)	9 (4.15)	148 (68.20)	10 (4.61)	< 0.001
RT-PCR test status						
Positive	440 (44.09)	74 (16.82)	17 (3.86)	344 (78.18)	5 (1.14)	
Negative	146 (14.63)	6 (4.11)	5 (3.42)	123 (84.25)	12 (8.22)	
Not tested	412 (41.28)	12 (2.91)	3 (0.73)	387 (93.93)	10 (2.43)	< 0.001
Symptoms						
Fever	545 (54.61)	50 (9.17)	8 (1.47)	476 (87.34)	11 (2.02)	0.053
Cough	666 (66.73)	63 (9.46)	15 (2.25)	583 (87.54)	8 (1.20)	< 0.001
Myalgia	301 (30.16)	22 (7.31)	3 (1.00)	271 (90.03)	5 (1.66)	0.039
Shortness of breath	573 (57.42)	58 (10.12)	21 (3.67)	477 (83.25)	17 (2.97)	0.022
SpO2 < 93%	612 (61.32)	61 (9.97)	17 (2.78)	513 (83.82)	21 (3.43)	0.166
Unconsciousness	31 (3.11)	4 (12.90)	7 (22.58)	12 (38.71)	9 (29.03)	< 0.001
Minor clinical criteria	185 (18.54)	13 (7.03)	3 (1.62)	166 (89.73)	3 (1.62)	0.343
Major clinical criteria	17 (1.70)	3 (17.65)	6 (35.29)	3 (17.65)	5 (29.41)	< 0.001
Co-existing disorders						
Cardiovascular disease	110 (11.02)	20 (18.18)	6 (5.46)	81 (73.64)	3 (2.73)	0.001
Diabetes	105 (10.52)	15 (14.29)	4 (3.81)	84 (80.00)	2 (1.91)	0.189
≥ 2 co-morbidities	80 (9.74)	15 (18.75)	5 (6.25)	55 (68.75)	5 (6.25)	< 0.001
Hypertension	57 (5.71)	7 (12.28)	5 (8.77)	41 (71.93)	4 (7.02)	0.001
Chronic pulmonary disease	30 (3.01)	4 (13.33)	1 (3.33)	23 (76.67)	2 (6.67)	0.435
Immunodeficiency	16 (1.60)	2 (12.50)	3 (18.75)	10 (62.50)	1 (6.25)	< 0.001
Chronic renal disease	10 (1.00)	2 (20.00)	2 (20.00)	6 (60.00)	0 (0.00)	0.002
Week of admission						
1st	116	8 (6.90)	4 (3.45)	100 (86.21)	4 (3.45)	
2nd	399	36 (9.02)	11 (2.76)	341 (85.46)	11 (2.76)	
3rd	483	48 (9.94)	10 (2.07)	413 (85.51)	12 (2.49)	0.903
Hospital type						
Teaching hospital	769 (77.05)	71 (9.23)	22 (2.86)	658 (85.57)	18 (2.34)	
High volume non-teaching	212 (21.24)	20 (9.43)	2 (0.94)	184 (86.79)	6 (2.83)	
Low volume non- teaching	17 (1.70)	1 (5.88)	1 (5.88)	12 (70.59)	3 (17.65)	0.005

[a] Values are expressed as a proportion (%) of the total number of patients for each week, as well as the total.
[b] The chi-square test was used to compare groups.
[c] Minor clinical criteria: Fever, cough, and myalgia.
[d] Major clinical criteria: Low SpO2, shortness of breath, unconsciousness.
[e] Immunodeficiency includes HIV infection and AIDS, cancer, immunodeficiency disorders, and receiving chemotherapy.
[f] Low volume hospitals indicate hospitals with less than 20 admitted COVID-19 patients.

the reference group (Table 3). In fact, the regression model showed that age affected death both independently and through a "corridor" of comorbidities. On the other hand, the adverse effects of major comorbidities were observed only in association with age, i.e., major comorbidities had no independent role in the CFR in this cohort of patients. In contrast, Guan et al. reported that, among hospitalized PCR-tested patients, the composite endpoint, including admission to ICU, invasive ventilation, and death, was higher in those who had known comorbidities (4). In addition, one meta-analysis previously reported that certain comorbidities were more prevalent in severe COVID-19 patients (5).

This study is among the first investigations aiming to frame the current picture of the battle with the initial phase of the COVID-19 outbreak in one of Iran's provinces. The main strength of this study is its timing, i.e., reporting the clinical patterns of hospitalized patients during the early period of the outbreak, when the medical system is presumed not to be overloaded. Additionally, acquiring data from the electronic data entry platform, which was designated exclusively to collect data of COVID-19 patients during their course of admission, along with the large sample size add to the robustness of the study results.

Table 3. Comparing the Study Patients Based on Their PCR-test Status [a, b, c]

Variables	RT-PCR Test Status			RT-PCR Test Results		
	Tested (N = 586)	Not Tested (N = 412)	P Value	Test Positive (N = 440)	Test Negative (N = 146)	P Value
Sex						
Female	243 (56.64)	186 (43.36)		188 (77.37)	55 (22.63)	
Male	343 (60.28)	226 (39.72)	0.248	252 (73.47)	91 (26.53)	0.283
Age group (y)						
< 50	221 (54.98)	181 (45.02)		168 (76.02)	53 (23.98)	
51 - 60	101 (52.60)	91 (47.40)		73 (72.28)	28 (27.72)	
61 - 70	119 (63.64)	68 (36.36)		90 (75.63)	29 (24.37)	
≥ 70	145 (66.82)	72 (33.18)	0.005	109 (75.17)	36 (24.83)	0.908
ICU admission						
Yes	39 (75.00)	13 (25.00)		22 (56.41)	17 (43.59)	
No	547 (57.82)	399 (42.18)	0.014	418 (76.42)	129 (23.58)	0.005
Co-existing disorders						
No	405 (55.25)	328 (44.75)		310 (76.54)	95 (23.46)	
Yes	181 (68.30)	84 (31.70)	< 0.001	130 (71.82)	51 (28.18)	0.222
≥ 2 Comorbidities	60 (75.00)	20 (25.00)	0.001	40 (66.67)	20 (33.33)	0.096
Cardiovascular diseases	80 (72.73)	30 (27.27)	0.002	56 (70.00)	24 (30.00)	0.258
Chronic pulmonary diseases	22 (73.33)	8 (26.67)	0.099	16 (72.73)	6 (27.27)	0.794
Diabetes	74 (70.48)	31 (29.52)	0.010	54 (72.97)	20 (27.03)	0.653
Hypertension	38 (66.67)	19 (33.33)	0.209	26 (68.42)	12 (31.58)	0.326
Immunodeficiency	9 (56.25)	7 (43.75)	0.840	5 (55.56)	4 (44.44)	0.172
Chronic renal diseases	7 (70.00)	3 (30.00)	0.466	5 (71.43)	2 (28.57)	0.822
Signs and symptoms						
Any sign	551 (57.22)	412 (42.78)	< 0.001	405 (73.50)	146 (26.50)	< 0.001
Fever	293 (53.76)	252 (46.24)	< 0.001	224 (76.45)	69 (23.55)	0.445
Cough	376 (55.90)	295 (44.10)	0.010	288 (77.01)	86 (22.99)	0.153
Myalgia	159 (52.82)	142 (47.18)	0.013	119 (74.84)	40 (25.16)	0.934
Shortness of breath	301 (52.53)	272 (47.47)	< 0.001	217 (72.09)	84 (27.91)	0.085
SpO2 < 93%	313 (51.14)	299 (48.86)	< 0.001	221 (70.61)	92 (29.39)	0.007
Unconsciousness	22 (68.75)	10 (31.25)	0.241	11 (50.00)	11 (50.00)	0.006
Outcome						
Recovery	484 (54.94)	397 (45.06)		349 (72.11)	135 (27.89)	
Death	102 (87.18)	15 (12.82)	< 0.001	91 (89.22)	11 (10.78)	< 0.001
Admission week						
1st	53 (45.69)	63 (54.31)		33 (62.26)	20 (37.74)	
2nd	249 (62.41)	150 (37.59)		200 (80.32)	49 (19.68)	
3rd	284 (50.80)	199 (41.20)	0.006	207 (72.89)	77 (27.11)	0.011

[a] Values are expressed as a proportion (%) of the total number of patients for each week, as well as the total.
[b] The chi-square test was used to compare groups.
[c] Immunodeficiency includes HIV infection and AIDS, cancer, immunodeficiency disorders, and receiving chemotherapy.

Table 4. Factors Associated with Death in Admitted COVID-19 Patients in Hospitals of Qazvin Province [a, b, c]

Subgroups	Number of Deaths (%)	Odds Ratio (95% CI)	P Value
Sex			
Female	48 (11.19)	Reference	
Male	69 (12.13)	1.16 (0.74, 1.81)	0.511
Age group (y)			
< 50	24 (5.97)	Reference	
50 - 59	12 (6.25)	0.97 (0.44, 2.11)	0.942
60 - 69	22 (11.76)	1.73 (0.89, 3.35)	0.101
≥ 70	59 (27.19)	5.15 (2.91, 9.12)	< 0.001
ICU admission			
No	92 (9.73)	Reference	
Yes	25 (48.08)	11.46 (5.53, 23.86)	< 0.001
RT-PCR test status			
Negative	11 (7.53)	Reference	
Positive	91 (20.68)	5.75 (2.65, 12.48)	< 0.001
Not tested	15 (3.64)	0.74 (0.30, 1.84)	0.531
Co-existing disorder			
Without co-existing disorder	67 (9.14)	Reference	
All	50 (18.87)	1.4 (0.91, 2.34)	0.110
≥ 2 Co-disorders	20 (25.02)	1.82 (0.92, 3.60)	0.081
Cardiovascular diseases	26 (23.64)	1.57 (0.86, 2.87)	0.186
Chronic pulmonary diseases	5 (16.67)	1.28 (0.43, 3.79)	0.438
Diabetes	19 (18.10)	1.39 (0.73, 2.64)	0.287
Chronic renal disease	4 (40.00)	3.07 (0.55, 17.08)	0.164
Immunodeficiency	5 (31.25)	4.3 (1.11, 17.23)	0.035
Hypertension	12 (21.05)	0.99 (0.44, 2.20)	0.991
Admission week			
1st	12 (10.34)	Reference	
2nd	47 (11.78)	0.77 (0.32, 1.75)	0.536
3rd	58 (12.01)	0.92 (0.41, 2.05)	0.845
Type of hospital			
Teaching hospitals	93 (12.09)	Reference	
High-volume non-teaching	22 (10.38)	0.61 (0.32, 1.11)	0.140
Low-volume non-teaching	2 (11.76)	0.23 (0.03, 1.55)	0.113

[a] A multivariate logistic regression analysis was performed to calculate the odds ratios (95% CIs).
[b] Immunodeficiency includes HIV infection and AIDS, cancer, immunodeficiency disorders, and receiving chemotherapy.
[c] Low-volume hospitals indicate hospitals with less than 20 admitted COVID-19 patients.

However, the findings on the clinical patterns and outcomes of the patients need to be interpreted in the context of our limitations. Among these caveats, we must emphasize the low availability of PCR testing in Iran. In addition, we did not have access to data on the patients' laboratory results, their smoking status, or the medications received. The external validity of our results needs further consideration. Our cohort study was conducted in all public and private sector hospitals in Qazvin province during the first three weeks since the epidemic began. Thereby, the generalization of our results to other populations should be carried out with caution.

The applied diagnosis and treatment flowchart, as was first proposed by the INIGCDT (3), merits further explanation. These guidelines, which have been mainly adapted from the World Health Organization (WHO) guidelines (6, 7), proposed chest imaging as the first diagnostic step to screen patients who require prompt hospitalization amid shortages in RT-PCR test kits in Iran. As a result, all admitted patients with suggestive COVID-19 symptoms, with or without comorbidities, underwent chest imaging (specifically a chest CT scan) in Qazvin hospitals. Among them, 59.3% were tested with RT-PCR, of whom 24.9% had negative results. This proportion of negative test results is in line with previous findings. While there has been a significant correlation observed between throat swab and sputum sample viral loads (8), one study examining the bio-distribution of SARS-CoV-2 in different body tissues reported positive RT-PCR rates in only 72% of sputum specimens (9).

Examining the concordance between chest CT scan and PCR test results, a previous study from Wuhan, China reported that chest CT sensitivity was 97% in RT-PCR-positive patients. On the other hand, in the PCR-negative patients, 75% had positive CT scan findings, 81% of whom were later considered as highly likely or probable cases of COVID-19 (10). Another study showed that the sensitivity of chest CT in diagnosing COVID-19 was significantly higher than RT-PCR in their patients (98 vs. 71%) (11).

When categorizing CT-diagnosed COVID-19 patients based on their RT-PCR test results, as expected, the worst scenario was reported in the group of patients with suggestive respiratory symptoms or underlying diseases who had positive PCR test results. These individuals accounted for 41% of ICU admissions throughout Qazvin province, with a 77% CFR, even after receiving ICU services. On the other hand, the group with negative PCR test results who had suggestive clinical symptoms or underlying diseases accounted for 32% of COVID-19-related ICU admissions in the province, among whom 71% recovered. It has been previously reported that negative PCR results may be due to lower viral load in patients' specimens (12, 13), which could provide a possible explanation for the lower CFR among the test-negative group. In the "no-test" group, which comprised CT-positive patients who were not tested for COVID-19 despite having suggestive clinical symptoms or coexisting diseases, 3.6% were admitted to ICUs, of whom 66.7% eventually recovered. The overall CFR between no-test group and patients with negative PCR results did not differ significantly. Based on the results of multilevel logistic regression analysis, in the first weeks of the epidemic, although PCR testing was more reserved for patients in a critical condition, its results should be presumed that a rather preemptive transfer of PCR positive patients to the ICU would partially explain the lower CFR in this group. Therefore, the criteria for ICU admission and prioritized allocation of the limited ICU beds should be identified (Table 5).

Table 5. Multi-level Regression Analysis to Compare in-Hospital Mortality Rate in Six Groups Based on PCR Test Results and ICU Admission

Group	In-Hospital Mortality (95% CI)	Odds Ratio (95% CI)	P-Value
Test negative/no ICU	6.1 (5.7, 6.9)	Reference	
Test positive/no ICU	19.0 (18.2, 19.8)	4.0 (1.8, 8.9)	0.001
No test/no ICU	3.5 (3.2, 3.7)	0.5 (0.2, 1.3)	0.202
Test negative/ICU	12.6 (11.9, 13.2)	2.3 (0.5, 10.4)	0.264
Test positive/ICU	44.4 (43.2, 45.6)	16.8 (5.6, 49.7)	< 0.001
No test/ICU	12.2 (11.6, 12.8)	2.2 (0.2, 20.7)	0.467

Additionally, there was a group of patients with negative PCR results who also lacked major clinical symptoms or significant comorbidities. These patients had the lowest CFR, and none of them were ICU-admitted. These non-COVID-19 hospitalized patients, who were not included in our analysis, may serve as a basis for comparing the admission course and outcomes of the study patients.

The importance of available ICU facilities in such an epidemic cannot be overemphasized. As officially announced by the Iranian Ministry of Health and Medical Education (MOHME) in 2018, there are a total of 8,264 ICU beds nationwide, and these were occupied by 453,891 patients during the year 2018 (occupancy rate: 55 patients/bed/year). In Qazvin province, which includes 1.6% of Iran's population, there are 96 ICU beds available (7.7 beds/100,000 of the population), comprising 1.1% of the total ICU beds in Iran. In this study, among the 92 non-survivors treated outside ICUs, 63% presented with shortness of breath, and 66% had low pulse oximetry readings. Among the 612 patients who presented an SpO2 of $< 93\%$, only 6.2% were admitted to ICUs. Considering that the ICU admission rate in this study was 5.2% (equal to 52 beds of total ICU beds in Qazvin province), it can be concluded that there is a need for at least 90 additional ICU beds throughout the province to save more lives. Interestingly, other studies have previously reported that while most COVID-19 patients present with a mild illness, about 14% progress to more severe forms of the disease and require hospitalization, with 5% needing ICU care (14-16).

We also need to briefly mention the RT-PCR testing process. Due to the considerable shortage of PCR test kits in

Iran, and according to the INIGCDT, physicians were encouraged to perform the test only in patients who were in a critical condition. Moreover, no re-testing was provided for patients with negative tests. While it has been reported that COVID-19 patients with more severe forms of the disease have higher viral loads and longer periods of viral shedding (6), the aforementioned testing protocol may have affected the results of the association between positive PCR test results and CFR.

In conclusion, we observed that COVID-19 patients hospitalized with mild symptoms, despite having positive chest CT changes and major comorbidities, were more likely to have negative rRT-PCR test results. Hence, there was a lower CFR and a more favorable outcome. Conversely, positive rRT-PCR test results were more prevalent in patients presenting with low SpO2 or unconsciousness, and they were strongly associated with increased odds of death among chest CT-positive patients. Considering the serious shortage in ICU capacity, preemptive transfer of more vulnerable rRT-PCR test-positive patients to the ICU might save their lives.

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Footnotes

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