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Clinical Features and Outcomes in Hospitalized Patients with COVID-19 in Northeastern Iran: A Retrospective Study of the Early Pandemic Period

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ABSTRACT

Background:
In this study, we described the demographic, clinical, radiological, laboratory, treatment, and outcome characteristics of hospitalized COVID-19 patients in Mashhad, northeastern Iran. These regional clinical data provide a historical record of disease presentation and outcomes.

methods:
In this retrospective cross-sectional study, we included confirmed COVID-19 patients hospitalized at two hospitals in Mashhad, Iran, between 20 February and 19 April 2020. Demographic, clinical, radiological, laboratory, treatment, and outcome data were extracted from medical records and analyzed using descriptive statistics and univariate tests.

Results:
Among 164 patients, 99 (60.4%) were male; 17 (10.4%) died during follow-up. The most common symptoms were dry cough, dyspnea, fatigue, sweats, and fever. The most common initial presenting symptoms were fever, chills, myalgia, fatigue, and cough. Bilateral lung involvement was seen in 95 (94.1%) of 101 patients who underwent chest imaging. The majority of patients received antibiotic therapy (92.7%). The most prevalent complications among fatal cases were ARDS, acute cardiac injury, and acute kidney injury.

Conclusions:
Men constituted a greater proportion of affected individuals. Older age and a history of cardiovascular disease were associated with mortality. Cough, dyspnea, and fatigue along with fever were considered as common symptoms. ARDS, acute cardiac injury, acute kidney injury, shock, and mechanical

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ventilation were observed more frequently among patients who died; these findings should be interpreted as markers or consequences of severe illness rather than evidence of causation. The treatment data describe historical practice during the study period and should not be interpreted as evidence of treatment efficacy.

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Introduction

Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the *Orthocoronavirinae* subfamily of the *Coronaviridae*. Coronaviruses mainly cause mild respiratory tract infections, but some strains have high infectivity and mortality posing a significant public health burden. For example, severe acute respiratory syndrome coronavirus (SARS-CoV) (1-3) and Middle East respiratory syndrome coronavirus (MERS-CoV), (4, 5) have caused more than 10,000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV (6, 7).
These two coronaviruses are zoonotic, and can be transmitted from animal to animal, animal to human, and human to human. Presumably, MERS-CoV transmission originated from bats to camels and then to humans, causing respiratory, enteric, hepatic, and neurologic diseases (8). Similarly, "SARS-CoV" was originated from bats, civet cats, and humans.

In December 2019, a cluster of acute respiratory illnesses, now known as novel coronavirus–infected pneumonia (NCIP), occurred in Wuhan, Hubei Province, China (9-13). The disease rapidly spread from Wuhan to other parts of China and subsequently to other countries in Asia, Europe, and the Americas. On January 7th, A novel coronavirus was identified by the Chinese Disease Control and Prevention (CDC) from a pharyngeal swab of a patient, and was subsequently named 2019-nCoV by WHO (14). In late January, the World Health Organization (WHO) declared the outbreak of this novel coronavirus as a global public health emergency for the sixth time in history (15). On January 31, 2020, this new strain of coronavirus labeled as 2019 novel coronavirus (2019-nCoV) was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of NCIP (16). 2019-nCoV is classified in the betacoronavirus 2b lineage, and broadly distributed in humans and other mammals (17). The 2019-nCoV infection cases were originated from bats among people living in or visiting Wuhan, China and human-to-human transmission has also been confirmed (18). The most common clinical presentation is fever, fatigue, dry cough, dyspnea, myalgia, leukocytopenia, and radiographic evidence of pneumonia. In severe cases, organ dysfunction including acute respiratory distress syndrome [ARDS], myocardial injury, renal damage, septic shock, and death can occur (19). However, there has been a great deal of heterogeneity in the clinical presentation, disease severity, diagnostic practice, and treatment across regions. of this disease. Although treatment strategies and clinical management have

subsequently evolved, early-pandemic clinical datasets remain useful for documenting regional disease patterns and outcomes and for understanding the initial clinical burden. In Iran, regional data from northeastern areas were limited during the first months of the outbreak. Therefore, we aimed to describe the clinical characteristics, laboratory and radiological findings, treatments, complications, and outcomes of hospitalized patients with confirmed COVID-19 in Mashhad, northeastern Iran.

Methods

Study design and participants

In this retrospective cross-sectional study, 164 patients who were admitted to Emam Reza and Ghaem Hospitals between 20 February 2020 and 19 April 2020 and diagnosed with COVID-19 according to the WHO interim guidance available at that time were enrolled.(20).

Procedures

We collected the following data from patient records: demographic information, past medical history, history of present illness, contact with suspected individuals, travel to high-risk locations, exposure to suspected people and high-risk locations, symptoms, physical examination findings, laboratory test results, chest computed tomographic (CT) scan findings, and treatment measures (i.e., antiviral therapy, corticosteroid therapy, respiratory support, kidney replacement therapy). The date of disease onset was defined as the day when patients reported first experiencing symptoms. Where data was missing from medical records or clarification was needed, we contacted the attending physician and other members of the patient's healthcare team. We also reached out to patients and their family members for any additional information that we could not obtain from the medical record or providers. We defined ARDS according to the Berlin definition (21). Acute kidney injury was diagnosed according to the Kidney Disease: Improving Global Outcomes Guidelines (22). Cardiac injury was defined as serum levels of cardiac biomarkers (e.g., troponin I) above the 99th percentile upper reference limit or as new abnormalities in electrocardiography and echocardiography (19). Clinical outcomes were followed until April 30, 2020. The duration from disease onset to hospital admission and onset of dyspnea as well as ARDS were recorded. All patients had a chest CT or plan chest radiograph or both. Typical features for COVID-19 pneumonia in CT scan were considered as those reported in the literature to be frequently associated with this condition. Diagnosis of 2019-nCoV was confirmed with PCR, lymphocyte count, CRP level, chest CT, and clinical symptoms at Mashhad University of Medical Sciences.

Ethical Approval

The study was approved by the Ethical Committee of Mashhad University of Medical Sciences. (Code: IR.MUMS.REC.1399.040). Written informed consent and verbal assent were obtained from patients involved before data collection.

Data analysis

Statistical analysis was carried out using SPSS, version 22. One sample t-test was used to compare differences in means in normal quantitative variables and expressed as mean ± standard deviation (SD). The Chi-square test was performed to compare strata expressed as numbers (percentages). A two-sided p-value <0.05 was considered statistically significant.

Results

In this cross-sectional study 164 patients hospitalized with confirmed NCIP. Baseline Demographic characteristics of subjects

were described in table1. There were a total of 164 participants, of whom approximately 99 (60.4%) were males and 65 (39.6%) females. The mean age of patients was 54.17 (range, 21-95 years old).

Table1: baseline demographic characteristics of 2019-nCoV-infected Patients

Variable		Patients (n=164)
Age, year		54.17±14.22
	≤39	25 (15.2%)
	40-49	36 (22%)
	50-59	39 (23.8%)
	60-69	37 (22.6%)
	≥70	25 (15.2%)
Sex	Female	65 (39.6%)
	Male	99 (60.4%)
Current smoker		7 (4.3%)
Hookah		8 (4.9%)
Narcotics		14 (8.5%)
Alcohol		2 (1.2%)
Travel		17 (10.4%)
Close contact with suspected person		34 (20.7%)
Comorbidities		20 (12.2%)
Diabetes		52 (31.7%)
Hypertension		48 (29.3%)
Cardiovascular Disease		38 (23.2%)
COPD		18 (11%)
Cancer		7 (4.3%)
Chronic hematologic disorder		1 (0.6%)
Immunodeficiency		1 (0.6%)
Asthma		9 (5.5%)

Corticosteroid use	7 (4.3%)
Rheumatoid arthritis	5 (3.0%)
Neurologic disorder	3 (1.8%)

COPD= Chronic obstructive pulmonary disease

The symptoms and clinical features of patients are shown in figure 1. In our sample, 136 (82.9%) individuals had upper respiratory tract symptoms (sputum production, anosmia, hyposmia, parosmia, dysgeusia, sore throat, rhinorrhea, nasal congestion), 154 (93.9%) had lower respiratory tract symptoms (dry cough, dyspnea, chest burning), and 104 (63.4%) had gastro-intestinal symptoms (diarrhea, nausea or vomiting, abdominal pain). The most common sign and symptoms were dry cough in 138 (84.1%), dyspnea in 132 (80.5%), fatigue in 129 (78.7%), sweating 119 (72.6%), fever in 110 (67.1%), headache in 100 (61.0%), and nausea or vomiting in 86 (52.4%) individuals. Upper respiratory tract symptoms or signs were seen in 60 (36.6%) individuals with 53 (32.3%) cases of anosmia, 48 (29.3%) cases of sore- throat, 45 (27.4%) cases of sputum production, 43 (26.2%) cases of sneezing, 35 (21.3%) cases of rhinorrhea, 32 (19.5%) cases of nasal congestion, hyposmia, and 12 (7.3%) cases of parosmia. The mean value of the highest temperature recorded for study participants was 37.58 ± 0.79°c (range, 36.30 - 41.00). Among subjects, 69 (42.1%) had a maximum recorded temperature below 37.4 °c, 66 (40.2%) had a maximum recorded temperature between 37.4-38.0 °c, 19 (11.6%) had a maximum recorded temperature between 38.1-39.0 °c, and 10 (6.1%) had a maximum recorded temperature above 39.0 °c. The mean oxygen saturation value was 87.62±8.91 %.

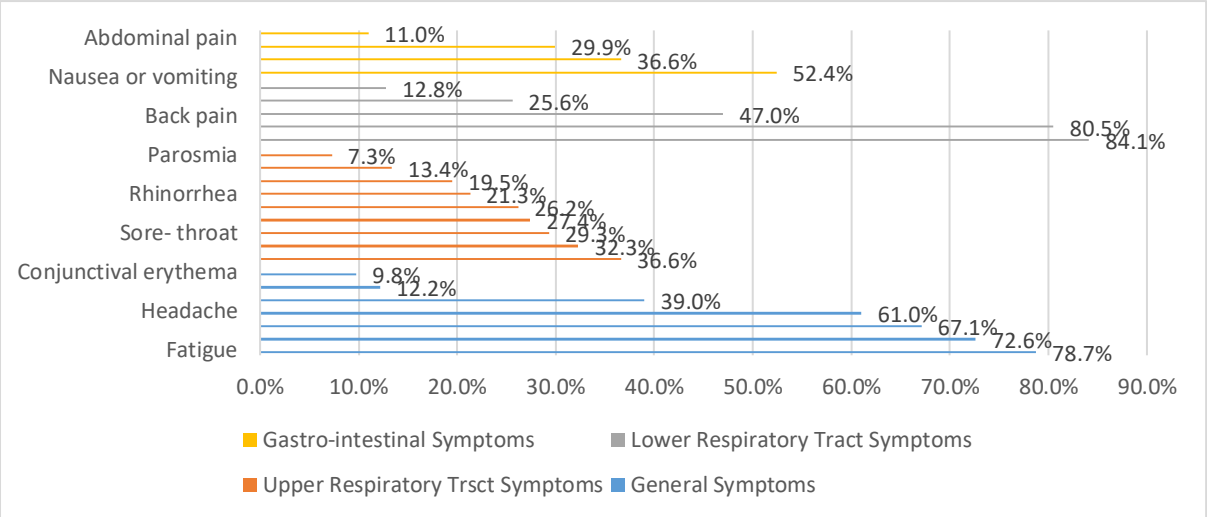

Figure1: Clinical features of 2019-nCoV-infected Patients

The five most common initial presenting symptom in individuals infected with 2019-nCoV was fever in 66 (40.2%), chills in 31 (18.9%), myalgia in 27 (16.5%), fatigue in 25 (15.2%), and cough in 21 (12.8%) individuals (Figure 2).

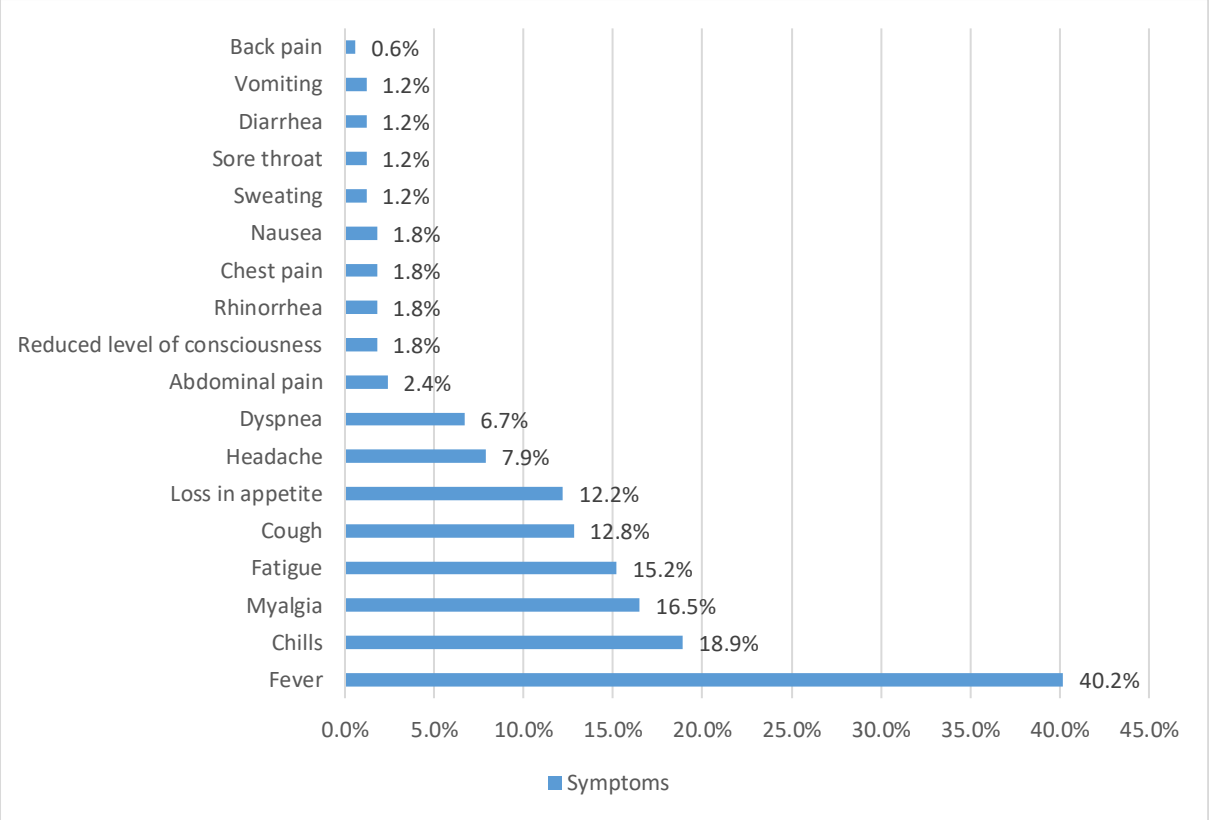

Figure2: First symptoms of 2019-nCoV-infected Patients

Table 2 shows the laboratory test results and imaging study findings of participants. The mean white blood cell count, lymphocyte count, platelets, and hemoglobin values at the time of admission were 7.11 $\times 10^3$ per µL, 1311.47 cells per µL, 203.15 $\times 10^3$ per µL, and 13.55 g/dl, respectively. A total of 101 patients had CT imaging of the chest and most of them 93 (92.1%) had typical features for COVID -19 pneumonia such as mixed ground glass opacities (GGO) and consolidation in 61 (61.6%), pure ground glass opacities (GGO) in 30 (30.3%) and consolidation alone in 8 (8.1%).

Most of lung lesions were likely to have a diffuse distribution 49 (51%), multifocal 45 (46.9%), and be 2 (2.1%) unifocal in patients. Bilateral lung involvement was seen in 95 (94.1%) subjects, four (4%) patients had a unilateral involvement which was confined to the right lung.

Table 2: clinical laboratory results and imaging data of 2019-nCoV-infected Patients

Variable	Patients (n=164)
White blood cell count, $\times 10^3$ per µL	7.11 (4.6-8.5)
Neutrophils, %	74.55 (68.20-82.70)
Lymphocyte count, cells per µL	1311.47 (840-1455)
Haemoglobin, g/dl	13.55 (12.20-15.02)

Platelets, $\times 10^3$ per µL		203.15 (151-231)
PTT, S		32.22 (29-34.55)
LDH, U/L		626.79 (429-758)
CRP, mg/L		69.40 (9-97)
ESR, mm/h		51.46 (28-76)
CT findings N=101	Normal	1 (1%)
	Typical	93 (92.1%)
	Atypical	4 (4%)
	Intermediate	3 (3%)
Bilateral lung involvement N=101		95 (94.1%)
Unilateral lung involvement N=99	Total	4 (4%)
	Right	4 (4%)
	Left	0 (0%)
Dominant pattern N=99	Mixed GGO and Consolidation	61 (61.6%)
	Consolidation	8 (8.1%)
	Pure ground glass opacification	30 (30.3%)
Lung antagonism N=96	Diffuse	49 (51%)
	Multifocal	45 (46.9%)
	Unifocal	2 (2.1%)

PTT= Activated Partial Thromboplastin Time, LDH=Lactate Dehydrogenase, CRP= C-reactive protein, ESR=Erythrocyte Sedimentation Rate, CT findings= Chest computed tomographic findings

The majority of patients in our sample received antibiotic therapy (92.7%). These treatments reflected the national/local protocol in use during the early pandemic and are reported descriptively rather than as evidence of treatment effectiveness. Antibiotics included vancomycin, meropenem, ceftriaxone, and clindamycin. 86.6% received antiviral treatment and 21.3% received corticosteroid. The antivirals including Azithromycin, Hydroxychloroquine, and lopinavir/ritonavir (reported in the original manuscript as Coltra), as well as oseltamivir and ribavirin. High-flow oxygen was administered in 79.3% of patients and 2.4% of individuals received oxygen through a nasal cannula. In addition, invasive mechanical ventilation was required in 2.4% of patients. Dialysis was performed in 4.3% of patients (Table3).

Table 3: Treatment regimen, complications and prognosis of 2019-nCoV-infected Patients

Variable		Patients (n=164)
Treatment	Antiviral treatment	142 (86.6%)
	Antibiotic treatment	152 (92.7%)
	Corticosteroid	35 (21.3%)
	Dialysis	7 (4.3%)
	Oxygen	130 (79.3%)
	Nasal canula	4 (2.4%)
	Non-invasive ventilation	6 (3.7%)
	Invasive mechanical ventilation	4 (2.4%)
Complications	ARDS	21 (12.8%)
	Acute cardiac injury	9 (5.5%)
	Acute kidney injury	7 (4.3%)
	Secondary infection	11 (6.7%)
	Shock	4 (2.4%)
	Death	17 (10.4%)
Prognosis	Days from the start of illness until hospitalization	8.69±5.80 (0-30)
	Days from start of illness until dyspnea	4.56±4.80 (0-29)
	Days from start of hospitalization until discharge	8.18±5.07 (0-28)

ARDS= Acute Respiratory Distress Syndrome

By the end of April 2020, the most common complications recorded were ARDS in 12.8% of participants (Table 3). According to the results of table 3, the mean number of days from the onset of symptoms to hospitalization and onset of dyspnea were 8.69±5.80 (range, 0-30 days) and 4.56±4.80 (range, 0-29 days), respectively. On average, individuals were hospitalized for 8.18 ± 5.07 (range, 0-28 days).

Table 4 describes coexisting conditions and complications among the 17 patients who died. These variables are presented as characteristics observed among fatal cases and should not be interpreted as causal determinants of death. The mean age was 65.71±16.29. Among the fatal cases, 1 (5.9%) was under 40 years, 4 (23.5%) were 50–59 years, 4 (23.5%) were 60–69 years, and 8 (47.1%) were ≥70 years. There was a statistically significant difference between age groups and death (P=0.001). Moreover,

the most prevalent complications among these individuals were ARDS in 12 (70.6%), acute cardiac injury in 6 (35.3%), and acute kidney injury in 3 (17.6%).

Statistically significant differences were seen between death and cardiovascular disease history, ARDS, acute cardiac injury, acute kidney injury, shock, invasive mechanical ventilation (P=0.002, P<0.001, P<0.001, P=0.004, P=0.004, P<0.001 respectively). Because these severe complications may occur as consequences or markers of disease severity, these associations are not interpreted as evidence that the complications caused death.

Table 4: coexisting disease, risk factors, and complications among 17 patients who died of COVID-19 pneumonia

Variable		Patients (n=17)	P-value
Age, year		65.71±16.29	0.001
	≤39	1 (5.9%)	
	40-49	0	
	50-59	4 (23.5%)	
	60-69	4 (23.5%)	
	≥70	8 (47.1%)	
Sex	Female	7 (41.2%)	0.891
	Male	10 (58.8%)	
Coexisting Risk Factors	Current smoker	7 (4.3%)	0.728
	Hookah	2 (11.8%)	0.164
	Narcotics	3 (17.6%)	0.156
	Alcohol	1 (5.9%)	0.197
	Comorbidities	3 (17.6%)	0.468
	Diabetes	5 (29.4%)	0.830
	Hypertension	7 (41.2%)	0.254
	Cardiovascular Disease	9 (52.9%)	0.002
	COPD	3 (17.6%)	0.353
	Cancer	1 (5.9%)	0.728
	Chronic hematologic disorder	0 (0%)	-
	Immunodeficiency	0 (0%)	-

	Asthma	0 (0%)	-
	Corticosteroid use	1 (5.9%)	0.725
	Neurologic disorder	0 (0%)	-
Complications	ARDS	12 (70.6%)	P<0.001
	Acute cardiac injury	6 (35.3%)	P<0.001
	Acute kidney injury	3 (17.6%)	0.004
	Secondary infection	2 (11.8%)	0.379
	Shock	3 (17.6%)	0.004

COPD= Chronic obstructive pulmonary disease, ARDS= Acute Respiratory Distress Syndrome

Discussion

In this retrospective study, we described 164 hospitalized patients with confirmed COVID-19 who were admitted to two tertiary referral hospitals in northeastern Iran during the early phase of the pandemic. The study should be interpreted in its historical context: treatment practices and clinical management have changed substantially since 2020. Nevertheless, the dataset provides a record of the clinical presentation, radiological findings, complications, and outcomes observed in this regional cohort.

We find in our study that males and individuals between the ages of 50-59 are more at risk for hospitalization of COVID-19. Our findings with regard to gender are consistent with many other studies, where the frequency of 2019 novel coronavirus infection was higher in men (19, 23-29). An explanation that has been discussed in other studies is that the prevalence of chronic diseases, especially diabetes and cardiovascular disease, are higher in men. However, there is evidence from recent studies in Iran suggesting a greater prevalence of hypertension, diabetes mellitus and cardiovascular disease in female populations (30, 31). Another possibility, which would explain the higher number of men in our sample is higher expression of ACE2, which is a major receptor for COVID-19, among males (32, 33). Another reason that women are less likely to fall ill with COVID-19 could be attributed to the protection conferred by the additional X chromosome and sex hormones, which have been shown to play an important role in innate and adaptive immunity (34). There has been some heterogeneity reported in the mean age of hospitalized individuals in different studies. Like us, several other investigators from China and Iran found that those in the 50-59 age group comprised the bulk of hospitalized patients (23, 24, 27, 29, 35), while others found individuals predominantly in the 40-40 (19, 26-28) or 60-69 age range in fatal cases (25). In a meta-analysis of 52251 patients the mean range of age was 49.5 years old and 53.7 % of patients was male (36), which does not deviate much from our results. The heterogeneity in mean age can be a result of a multitude of factors. For example, some studies have looked at hospitalized patients while others examine outpatients, where one expects to see younger individuals. Another factor that is likely to influence these findings is the age composition of the population. Iran has a younger population than countries like Italy where the mean age of hospitalized individuals was 54.17.

In our study, 8.5% of participants reported narcotic use, which was higher than the proportion of individuals who were current

smokers, hookah users, or who consumed alcohol. Because this was a retrospective observational study with a limited number of deaths, the observed frequencies should not be interpreted as evidence that narcotic use is an independent risk factor for severe COVID-19 or mortality. Larger prospective or adequately adjusted studies would be required to evaluate such associations. In our patient population, diabetes, hypertension, and cardiovascular disease were the most common coexisting medical conditions. Diabetes has been identified as the most common risk factor for the severity of COVID-19 disease in a number of studies (19, 35, 36) while in others, hypertension was more common (23, 26-28). These differences could in part be explained by differences in ethnicity.

The most common symptoms in our study were dry cough, dyspnea, fatigue, sweating, and fever. These findings are consistent with early-pandemic reports describing fever, cough, dyspnea, fatigue, and myalgia among hospitalized patients. The comparison is useful for documenting the clinical phenotype observed in our region during the early pandemic, rather than for guiding current clinical management. A study by Bernheim and colleagues recently revealed that among 121 patients with COVID-19, fever, cough and sputum production were the most common clinical symptoms (37). In another study, among 41 COVID-19 admitted patients the common symptoms at onset of illness were fever 40 (98%), cough 31 (76%), and myalgia or fatigue 18 (44%) (19). Similarly, in a study conducted by Wang and colleagues, fever was the most common symptom, seen in virtually all patients while fatigue and dry cough were also observed in nearly 70 and 60 percent of patients, respectively (23). Lui and colleagues also found that among 137 COVID-19 patients, the most common symptoms were fever (81.8%), cough (48.2%), myalgia or fatigue (32.1%) (35). There is only one other study in Iran of 105 patients with severe COVID-19 pneumonia, in which 83% reported dry cough, 78.1% reported fever, and 72.4% reported dyspnea. Myalgia 51 (48.6%), and fatigue 29 (27.6%) were also commonly reported in these individuals (29). In another study, only 43% of patients had fever at admission and another 88.7% developed fever during their hospitalization (28). Taken together with other studies, our findings indicate that cough, dyspnea, and fatigue may have the greatest diagnostic value among symptoms, as fever seems to be more transient.

In our patient population, the most common initial symptoms of illness were fever (40.2%), chills (18.9%), myalgia (16.5%), fatigue (15.2%), and cough (12.8%). In the another Iranian study, 49.5% and 23.8% exhibited fever and cough as their first symptom, respectively (29).

On imaging, bilateral involvement was seen in 94.1% of those who had a chest CT, while only 4% had unilateral lung involvement. The dominant pattern was mixed GGO and consolidation in 62% of cases. Our results are consistent with several other studies that show bilateral involvement as being most common (19, 23, 24, 35).

In our study, antibiotic therapy was administered to 92.7% of patients, while antiviral therapy was recorded in 86.6%. Antibiotic therapy was administered more in our study compared to some other studies (19, 35). Antiviral therapy was used more commonly by others (23, 24). As with most other studies, ARDS was the most common complication we observed (19, 23, 24). These figures describe treatment practice during the early pandemic and the protocol used at the participating hospitals. They should not be interpreted as evidence that

these treatments were effective. Subsequent evidence and changes in clinical guidelines mean that the treatment patterns observed in this historical cohort are not necessarily applicable to current COVID-19 management.

Furthermore, the mean number of days from disease onset to hospitalization, the onset of dyspnea, and the duration of hospitalization was similar in our study and another(19). Accordingly, Dyspnea was a most common reason for patients to refer to the hospital. Furthermore, the mean of days starting illness onset discharge is almost 17 days. The mean intervals from symptom onset to hospitalization, onset of dyspnea, and discharge provide additional information about the clinical course observed in this early-pandemic cohort. These measures should be interpreted as descriptive characteristics of the study population rather than as estimates applicable to contemporary SARS-CoV-2 infections.

Conclusion

Our results show that older age and cardiovascular disease history were associated with mortality. Furthermore, men constituted a greater proportion of those being admitted to the hospital for COVID-19. We propose that cough, dyspnea, and fatigue along with fever be considered as common presenting symptoms. Our findings reveal that diabetes is the most common coexisting medical conditions in COVID-19 patients. Severe complications, including ARDS, acute cardiac injury, acute kidney injury, and shock, were more frequently observed among patients who died; however, because these events can reflect advanced disease severity, causal conclusions cannot be drawn. The findings describe hospitalized patients during the early phase of the COVID-19 pandemic in northeastern Iran and should not be interpreted as a description of current treatment standards.

Limitations

This study has several limitations. It was retrospective, conducted at two hospitals, and included a relatively small number of deaths (n=17). The statistical analyses were primarily univariate; therefore, residual confounding, including confounding by age and overall disease severity, cannot be excluded. In particular, severe complications such as ARDS, shock, cardiac injury, and mechanical ventilation may represent consequences or markers of severe disease rather than independent predictors of mortality. In addition, the treatment data reflect early-pandemic practice and should not be interpreted as treatment efficacy.

Authors' contribution

All authors read and approved the final version of the manuscript.
MB: Project management, paper editing

MBA: Project management, Data analysis, proposal and paper writing

ZM, RKT, FM, PL, MA: Data collection

MN: Project management

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Conflict of interest

All authors declare any competing interests.

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