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CLINICAL STUDY

Risk factors for mortality of 557 adult patients with COVID 19 in Babol, Northern Iran: a retrospective cohort study

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ABSTRACT

BACKGROUND: This study was aimed to investigate the risk factors for mortality in patients with COVID-19.

METHODS: For this retrospective cohort study, we included 121 deceased and 436 discharged cases with COVID-19 in Babol, Northern Iran. The cases were between March 1 to April 1, 2020.

RESULTS: Multivariate Poisson regression analysis revealed that older age (aRR: 1.03, 95% CI: 1.01, 1.05, p < 0.001), hospital length of stay (aRR: 0.94, 95% CI: 0.90, 0.97, p = 0.003), ICU admission (aRR: 4.34, 95% CI: 2.95, 6.37, p < 0.001), cerebrovascular disease (aRR: 1.96, 95% CI: 1.20, 3.19, p = 0.007), ventilator-associated pneumonia (VAP) (aRR: 2.09, 95% CI: 1.22, 3.55, p = 0.006), septic shock (aRR: 2.98, 95% CI: 1.44, 6.19, p = 0.003), acute respiratory distress syndrome (ARDS) (aRR: 3.80, 95% CI: 2.28, 6.31, p < 0.001), acute kidney failure (AKF) (aRR: 1.45, 95% CI: 1.12, 3.76, p = 0.021), acute heart failure (AHF) (aRR: 1.63, 95% CI: 1.01, 2.62, p = 0.043) and lymphocyte count (aRR: 3.01, 95% CI: 1.99, 4.57, p < 0.001) were associated with mortality.

CONCLUSION: Findings showed that elderly with comorbidities such as cerebrovascular diseases had an increased risk of death. Some complications such as: pneumonia, septic shock, ARDS, AHF, and AKF played crucial roles as well death *(Tab. 2, Ref. 25)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, mortality, clinical characteristics, laboratory findings.

Introduction

In late December 2019, local health authorities reported many cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) of unknown cause, which were possibility related to wet markets in Wuhan, a city in China's Hubei province (1, 2). The infection spread quickly across the globe. Subsequently, the 2019 novel coronavirus (COVID-19) was reported as a global health emergency by the end of January 2020 (3). In early January of 2020, COVID-19 was first isolated from some cases and confirmed as the cause of the NCIP. COVID-19 was classified in the betacoronavirus lineage 2b (4). Several reports described that COVID-19 had about 80 % homology with severe acute respiratory syndrome-related coronavirus (SARS-CoV). Also, the homology between the COVID-19 genome and the bat SARS-like coronavirus genome is greater than 90 % (5). Studies showed that the clinical features of COVID-19 may range from asymptomatic to multi-organ failure (e.g., acute respiratory distress syndrome (ARDS), shock, acute cardiac injury, acute kidney injury, and acute liver injury) and admission to the intensive care unit (ICU) and death (6). In the other words, most common clinical characteristics of COVID-19 included: fever, chills, non-productive cough, shortness of breath, muscle pain, and lymphopenia, along with some radiographic findings of pneumonia (7, 8). Mortality rates were reported in several studies. In the retrospective case series study, Chen et al reported 799 cases with COVID-19. This research showed that 113 patients died (overall mortality of up to14 %) and 161 cases discharged [Chen, 2020 #1](9). Despite several studies on COVID-19, clinical data from deceased cases did not appear to be sufficient. This may be due to the insufficient number of cases being examined. This study reported the clinical characteristics of COVID-19 patients admitted to 3 hospitals in Babol, Iran and factors associated with mortality.

Methods

Study design, ethical considerations, and participants

The current study protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (Code: IR.

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MUBABOL.HRI.REC.1398.349). Five hundred fifty-seven cases with confirmed COVID-19 admitted to 3 central hospitals affiliated to Babol University of Medical Sciences from March 1 to April 1, 2020, were enrolled. All cases with COVID-19 enrolled in the recent research were diagnosed according to WHO interim guidance for 2019 novel coronavirus (6th edition) (10). In other words, all patients with physician- and laboratory-confirmed (positive in nasopharyngeal/ throat swab specimens by reverse transcription polymerase chain reaction (RT-PCR)) COVID-19 infection were included, while suspected cases with similar clinical symptoms were excluded from this study. All recovered patients with COVID-19 had completely resolved signs and symptoms, had a significant improvement in pulmonary (blood oxygen saturation (SpO2) ≥ 93 %) and extrapulmonary organ dysfunction, and no longer needed a supportive care before hospital discharge. The requirement for an informed consent was waived because of the emergency conditions of this disease. These treatment centres cover a large population of people living in Mazandaran province, North of Iran. Over the course of the COVID-19 pandemic, 410 beds have been allocated across the board to treat COVID-19 patients and ICU capacity at our hospitals was increased to 60 beds. The clinical outcomes such as hospital discharge, length of stay, and death were followed up to April 20, 2020.

Tab. 1. Baseline characteristics of 557 patients hospitalized in 3 central hospitals affiliated to Babol University of Medical Sciences with COVID-19.

	All patients (n=557)	Deceased patients (n=121)	Survivor patients (n=436)	p*
Age, mean (SD), y	60.2 (15.3)	67.9 (13.9)	58.0 (15.0)	< 0.001
Sex				
Male	305 (54.7)	75 (61.9)	230 (52.7)	0.071
Female	252 (45.1)	46 (38.0)	206 (47.1)	
Comorbidities				
Hypertension	148 (26.5)	44 (36.3)	104 (23.8)	0.006
Diabetes	161 (28.9)	43 (35.5)	118 (27.0)	0.069
Malignancy	27 (4.8)	10 (8.2)	17 (3.8)	0.048
Cardiovascular disease	131 (23.5)	36 (29.7)	95 (21.7)	0.068
Chronic kidney disease	21 (3.7)	5 (4.1)	16 (3.6)	0.813
Liver disease	6 (1.0)	1 (0.8)	5 (0.9)	0.763
Cerebrovascular disease	15 (2.6)	6 (4.9)	9 (2.0)	0.082
COPD	18 (3.2)	5 (4.1)	13 (2.9)	0.527
Signs and symptoms				
Fever	360 (64.6)	69 (57.0)	291 (66.7)	0.048
Fatigue	269 (48.2)	55 (45.4)	214 (49.0)	0.480
Dry cough	353 (63.3)	68 (56.2)	285 (65.3)	0.064
Anorexia	216 (38.7)	39 (32.2)	177 (40.6)	0.095
Myalgia	109 (19.5)	17 (14.0)	92 (21.1)	0.084
Dyspnoea	399 (71.6)	92 (76.0)	307 (70.4)	0.225
Expectoration	142 (25.4)	20 (16.5)	122 (27.9)	0.011
Pharyngalgia	68 (1.2)	7 (5.7)	61 (13.9)	0.015
Diarrhoea	42 (7.5)	2 (1.6)	40 (9.1)	0.006
Constipation	39 (7.0)	11 (9.0)	28 (6.4)	0.309
Haemoptysis	10 (1.7)	0 (0)	10 (2.2)	0.093
Dizziness	100 (17.9)	18 (14.4)	82 (18.8)	0.319
Headache	128 (22.9)	15 (12.4)	113 (25.9)	0.002
Vomiting	154 (27.6)	25 (20.6)	129 (29.5)	0.128
Abdominal pain	66 (11.8)	10 (8.2)	56 (12.8)	0.168
Chest pain	109 (19.5)	17 (14.0)	92 (21.1)	0.084
Anosmia	36 (6.4)	3 (2.48)	33 (7.5)	0.044
Hospital admission median (IQR), d	6 (10, 4)	6 (10, 3)	6 (10, 4)	0.819
Heart rate, median (IQR), bpm	80 (88, 80)	83 (100, 80)	80 (100, 80)	<0.001
Respiratory rate, median (IQR)	20 (21, 20)	20 (22, 19)	20 (22, 19)	0.627
Arterial pressure, median (range), mm Hg	115.8 (130.7, 105.6)	113.1 (130.8, 100.8)	120.6 (130.6, 110.6)	0.743
Complications				
ARDS	8 (1.4)	4 (3.3)	4 (0.9)	0.051
Acute cardiac injury	31 (5.5)	24 (19.8)	7 (1.6)	<0.001
Arrhythmia	13 (2.3)	11 (9.0)	1 (0.2)	<0.001
Ventilator-associated pneumonia	15 (2.6)	5 (4.1)	10 (2.2)	0.269
White blood cell count, $\times 10^9$/L	7.4± (3.8)	9.7± (4.0)	7.0± (4.0)	<0.001
Lymphocyte count, $\times 10^9$/L	2.1± (1.0)	1.3± (0.9)	2.3± (1.0)	<0.001
C-reactive protein (mg/L)	7.7± (5.9)	10.3± (6.8)	7.1± (5.4)	<0.001

p values of the variables comparing deceased and survivors are from t-test. Data are n (%) unless otherwise stated.
ARDS – acute respiratory distress syndrome

Data Collection

The patient´s medical records were investigated by an experienced team of researchers and physicians of Infectious Diseases Research Center of Babol University of Medical Sciences. The epidemiological, clinical, laboratory, and radiological findings, medications and outcomes information were collected with a data collection checklist from the electronic medical records. Moreover, the recorded data of patients comprised demographic information, past medical history (PMH), underlying medical conditions, signs, symptoms, para clinical data, and treatments (i.e., antivirals, antibiotics corticosteroids, breathing supports).

Statistical analysis

Continuous variables were described by the mean (SD) or median (IQR) as appropriate. Categorical variables were described by counts (percentages). Clinical features of the discharged and deceased patients were compared using the Chi-square test for categorical variables and Student's t-test for continuous variables. We estimated the adjusted risk ratios (aRRs) and 95 % CIs for the association between the clinical features and mortality using the Poisson regression model. The results showed by the adjusted risk ratio (aRR) with 95 % CIs. The following variables were included in the model: age, gender, hospital length of stay, ICU admission, co-

morbidities, laboratory markers, vital signs (10). Statistical analyses were performed on Stata 16.0 (Stata Corp, College Station, TX, USA). All statistical tests were two-tailed at the significance level of $p < 0.05$.

Results

A total of 557 adult patients (aged ≥ 16 years) with a confirmed COVID-19, were enrolled in the study, including 436 (78.28 %, 95% CI: 74.85, 81.70), who were discharged and 121 (21.72 %, 95% CI: 18.29, 25.14), who died. Table 1 shows the baseline clinical features of the patients. All 557 enrolled patients showed a bilateral involvement of chest CT scans. The median age of the patients was 61 years (IQR: 71, 50.75), ranging from 16 years to 97 years, and 45.1 % of patient were female. The median duration of hospital length of stay was 6 days (IQR: 10, 4), ranging from one day to 34 days. As expected, the deceased patients were significantly older (MD: 9.91, 95% CI: 6.83, 13.01; $p < 0.001$) and were more likely to have underlying diseases, including hypertension (RR: 1.57, 95% CI: 1.14, 2.17; $p = 0.005$), malignancy (RR: 1.76, 95% CI: 1.05, 2.97; $p = 0.047$), cerebrovascular diseases (RR: 1.88, 90% CI: 1.10, 3.22; $p = 0.081$), and cardiovascular diseases (RR: 1.37, 90% CI: 1.03, 1.82; $p = 0.067$). Of the total patients, 399 (94.79 %, 95% CI: 92.94, 96.63) had symptoms with dyspnoea (71.63 %) being the most common symptom, followed by fever (64.63 %), dry cough (63.37 %) and fatigue (48.29 %). While 44 (36.36 %, 95% CI: 27.79, 44.93) of deceased patients had deteriorated vital signs, only 22 (5.04 %, 95%CI: 2.99, 7.10) of the discharged patients had adverse vital signs ($p < 0.001$). Among all patients, 134 (24.05 %, 95 %CI: 20.50, 27.60) were admitted with SpO_2 less than 90 %. The heart rate of the deceased patients was significantly higher than values of those, who were discharged (MD: 6.63, 95% CI: 3.49, 9.17; $p < 0.001$). Also, the mean of SpO_2 was significantly lower than the values of those, who were discharged (MD: –5.66, 95% CI: –7.82, –3.51; $p < 0.001$). Laboratory results showed that there were significant differences in the white blood cell counts (MD: 2.75, 95% CI: 1.84, 3.65; $p < 0.001$), absolute values of lymphocytes (MD: –1.01, 95% CI: –1.23, –0.76; $p < 0.001$) and C-reactive protein (CRP) (MD: 3.26, 95% CI: 1.90, 4.62; $p < 0.001$) between the two groups. Table 2 shows the association between clinical features of the patients and mortality of COVID-19 infection. For every day of hospital stay increase, the risk of death decreased by 6% (aRR: 0.94, 95% CI: 0.90, 0.97, $p = 0.003$). We found a strong positive association between ICU admission and COVID-19 mortality (aRR: 4.34, 95% CI: 2.95, 6.37, $p < 0.001$). Patients with lymphopenia showed a significantly higher risk of death compared to normal lymphocyte count (aRR: 3.01, 95% CI: 1.99, 4.57, $p < 0.001$). As the result, WBC counts (aRR: 1.29, 95% CI: 0.85, 1.94, $p = 0.224$) and CRP levels (aRR: 1.32, 95% CI: 0.39, 4.48, $p = 0.651$) were ruled out as a risk factor for the COVID-19 mortality. Compared to the patients with appropriate vital signs, the risk of death was significantly higher in patients with ventilator-associated pneumonia (VAP) (aRR: 2.09, 95% CI: 1.22, 3.55, $p = 0.006$), septic shock (aRR: 2.98, 95% CI: 1.44, 6.19, $p = 0.003$), ARDS (aRR: 3.80, 95% CI: 2.28, 6.31, $p < 0.001$), acute heart failure (AHF) (aRR: 1.63, 95% CI: 1.01, 2.62, $p = 0.043$) and acute kidney failure (AKF) (aRR: 1.45, 95% CI: 1.12, 3.76, $p = 0.021$). In addition, compared to the patients without comorbidities, the risk of COVID-19 mortality was also significantly higher among the patients with a history of cerebrovascular diseases (aRR: 1.96, 95% CI: 1.20, 3.19, $p = 0.007$). The adjusted RR for other comorbidities in association with COVID-19 mortality was not estimated due to a sparse data and rare exposure. The association between gender and COVID-19 mortality was not significant (aRR: 1.09, 95 % CI: 0.73, 1.62, $p = 0.662$). Multivariable Poisson regression analysis revealed that older age (aRR: 1.03, 95% CI: 1.01, 1.05, $p < 0.001$) was independently associated with hospital mortality. In our country, based on the standard treatment protocol, Kaletra (lopinavir/ ritonavir), hydroxychloroquine sulfate and chloroquine phosphate drugs were prescribed for COVID-19 patients. However, in some patients, medications such as interferons and antibiotics were also prescribed due to lack of appropriate response to treatment. Therefore, all the patients received antiviral treatment, including a single 400 mg oral dose of hydroxychloroquine sulfate, or a single 500 mg oral dose of chloroquine phosphate along

Tab. 2. Factors associated with mortality among COVID-19 patients.

	Crude RR (95% CI)	p	Adjusted RR (95% CI)	p
Age in years	1.03 (1.02, 1.04)	< 0.001	1.03 (1.01, 1.05)	< 0.001
Gender				
Female	Ref		Ref	
Male	1.37 (0.98, 1.90)	0.061	1.09 (0.73, 1.62)	0.662
Hospital length of stay, days	0.99 (0.96, 1.03)	0.842	0.94 (0.90, 0.97)	0.003
ICU admission	4.24 (3.25, 5.53)	< 0.001	4.34 (2.95, 6.37)	< 0.001
Hypertension	1.57 (1.14, 2.17)	0.005	1.01 (0.68, 1.47)	0.969
Cerebrovascular disease	1.88 (0.99, 3.57)	0.053	1.96 (1.20, 3.19)	0.007
Pneumonia	1.55 (0.74, 3.24)	0.227	2.09 (1.22, 3.55)	0.006
Septic shock	4.66 (3.97, 5.46)	< 0.001	2.98 (1.44, 6.19)	0.003
ARDS	5.58 (4.65, 6.70)	< 0.001	3.80 (2.28, 6.31)	< 0.001
AHF	4.19 (3.23, 5.45)	< 0.001	1.63 (1.01, 2.62)	0.043
AKF	3.10 (1.37, 7.02)	0.007	1.45 (1.12, 3.76)	0.021
WBC				
≤ 11 count, $\times 10^9$/L	Ref		Ref	
> 11 count, $\times 10^9$/L	2.83 (2.01, 3.97)	<0.001	1.29 (0.85, 1.94)	0.224
Lymphocyte				
≤ 1 count, $\times 10^9$/L	Ref		Ref	
> 1 count, $\times 10^9$/L	4.64 (3.39, 6.35)	<0.001	3.01 (1.99, 4.57)	<0.001
CRP				
≤ 10 mg/L	Ref		Ref	
> 10 mg/L	2.25 (0.75, 6.76)	0.145	1.32 (0.39, 4.48)	0.651

P values of the variables comparing deceased and survivors are from t-test. Data are n (%) unless otherwise stated. ICU – intensive care unit, ARDS – acute respiratory distress syndrome, AHF – Acute heart failure, AKF – acute kidney failure, WBC – white blood cells, CRP –C-reactive protein

with Kaletra two 200 mg tablets BD, for 5–14 days. Furthermore, cephalosporins and glycopeptide antibiotics were also used for some patients with suspected staphylococcal infections.

Discussion

The current study described the main differences in clinical presentations between deceased patients with COVID-19 and those, who survived. The mean age of deceased cases was older than that of recovered cases. This study showed a direct association between ICU admission and mortality. Lymphopenia was more common in deceased patients than in recovered patients. The risk of death was higher in patients with VAP, septic shock, ARDS, AHF and AKF. Also, the risk of COVID-19 mortality was higher among cases with a history of cerebrovascular diseases. The results of such studies contribute to our knowledge of the factors affecting the mortality. As the result, it will speed up diagnostic and treatment processes of the patients and reduce mortality as well. The clinical spectrum of COVID-19 varies from asymptomatic forms to death (11). Here, the recent study including some clusters of patients showed a considerable mortality rate for COVID-19. This is partly due to a large proportion of critically ill cases admitted to our hospitals at this time. It is important to note, that the mortality rate of COVID-19 is lower than for SARS-CoV and MERS-CoV (12). Though, COVID-19 has verified more deadly for different reasons, such as commonly transition through direct person-to-person contacts and atypical symptoms at during early-stage infection (13, 14). Yang et al reported that the mortality rate in critically ill cases with COVID-19 was higher than that in critically ill patients with SARS-CoV (15). The overall mortality rate for confirmed COVID-19 patients was found to be higher in elderly (16, 17). In other words, elderly patients are at high risk of fatality with COVID-19. It was agreed with our results, that the age of deceased patients was higher than that of the survivors. There are several reasons for this issue such as: age-related decline in immune function and chronic comorbidities due to their weaker immune system (16). Moreover, based on the latest researches on clinical features of COVID-19 patients who required ICU admission, coexisting conditions, and elderly, are believed to be serious risk factors for death. As such, a high-quality monitoring seems necessary for the patients at risk. In our study, of the total cases, 399 had symptoms with dyspnoea (71.63 %) being the most common symptom, followed by fever (64.63 %), dry cough (63.37 %) and fatigue (48.29 %). The incidence of symptoms including fever, expectoration, pharingalgia, diarrhoea, headache, and anosmia differed significantly between the non-survivors and recovered cases. These results were consistent with other researches, which showed common symptoms including: fever, fatigue, and dry cough (18). Moreover, recently there have been cases of gastrointestinal involvement such as diarrhoea and abdominal pain reported with COVID-19 (19). Also, the vital signs records showed that most deceased patients had tachycardia as well as lower SpO_2 than the survivors. These signs and symptoms indicated that most deceased cases had been in a critical condition on admission. Therefore, clinicians should pay special attention to such symptoms, when dealing with this infection, because they can cause undesirable results with poor outcomes.

Some abnormalities of laboratory results between the deceased and recovered cases were considerable. Most of the dead cases developed severe lymphopenia. The presence of lymphopenia as a signature of severe COVID-19 was confirmed by many other studies. The researches suggested that the endothelial dysfunction induced endothelial cell death, blood-tissue barrier destruction, and leukocyte adhesion, which might describe the lymphopenia in severe COVID-19 (20). Moreover, other common laboratory abnormalities in deceased patients included leucocytosis and high CRP levels. However, by adjusting the various possible factors influencing these laboratory findings, we did not conclude that they are considered a risk factor for death. On the other hand, due to the small number of dead patients, this may be justified.

In the recent study, some complications such as: VAP, septic shock, ARDS, AHF, AKF, and comorbidities as cerebrovascular diseases were higher in deceased patients. Other studies showed that deceased cases might develop pulmonary and extrapulmonary organ dysfunctions, comprising like ARDS, acute kidney injury, sepsis, acute cardiac injury, shock, and acute liver injury in the later stages of COVID-19 (21). Among them, respiratory and neurological system complications along with the cardiac disorders were associated with a poor outcome (22). All of these warn physicians that particular attention should be paid to other complications, especially neurological and cardiac involvements, along with examining respiratory complications.

As yet, there are no drugs or vaccines approved to treat or prevent COVID-19 except some supportive therapies (23–25). In other words, for now the approach to COVID-19 include the control of possible sources of infection, decrease transmission probability between people, timely diagnosis, and treatments. Also, treatment with antibacterial agents seemed to be ineffective. In the present study, like many other studies, VAP has been suggested as an important factor in patient mortality. Therefore, in order to treat this infection and prevent the spread of antibiotic resistance, it is better to prepare appropriate guidelines on empirical antibiotic use in COVID-19 cases. The current study had some limitations. The relatively small sample size especially for non-survivors made it difficult to draw accurate conclusions. Thus, it is advisable to use bigger sample size in consequent researches to more accurately measure the association between several variables. Secondly, due to the retrospective study design, all laboratory tests were not estimated in all cases. It is primarily limited by being a retrospective analysis of laboratory data. Multiple clinicians were responsible for contributing to the administrative record, and the data were not validated by any central authority. In contrast, this study also had several strengths .It is a cohort study, so the first condition of causality, i.e. temporality, was realized. Also, in this study, detailed important variables for assessing the causal association among clinical features and in hospital mortality were gathered. Finally, we confront the confounding phenomenon by multivariate modified Poisson regression, and we estimated the risk ratio directly.

Conclusions

Our data revealed that older patients with comorbidities such as cerebrovascular diseases had an increased risk of death with COVID-19. Some complications such as pneumonia, septic shock, ARDS, AHF, and AKF were associated with in-hospital mortality. It is also important to note that lymphopenia can be a signature of severe COVID-19 especially in deceased patients.

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