Clinical and laboratory findings from patients with COVID-19 pneumonia in Babol North of Iran: a retrospective cohort study

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Background. In December 2019, China has experienced an outbreak of novel coronavirus disease 2019 (COVID-19). Coronavirus has now spread to all of the continents. We aimed to consider clinical characteristics, laboratory data of COVID-19 that provided more information for the research of this novel virus.

Methods. We performed a retrospective cohort study on the clinical symptoms and laboratory findings of a series of the 100 confirmed patients with COVID-19. These patients were admitted to the hospitals affiliated to Babol University of Medical Sciences (Ayatollah Rohani, Shahid Beheshti and Yahyanejad hospitals) from 25 February 2020 to 12 March 2020.

Results. Nineteen patients died during hospitalization and 81 were discharged. Non-survivor patients had a significantly higher C-reactive protein (CRP) (MD: 46.37, 95% CI: 20.84, 71.90; $P = 0.001$), white blood cells (WBCs) (MD: 3.10, 95% CI: 1.53, 4.67; $P < 0.001$) and lower lymphocyte (MD: -8.75, 95% CI: -12.62, -4.87; $P < 0.001$) compared to survivor patients. Data analysis showed that comorbid conditions (aRR: 2.99, 95% CI: 1.09, 8.21, $P = 0.034$), higher CRP levels (aRR: 1.02, 95% CI: 1.01, 1.03, $P = 0.044$), and lower lymphocyte (aRR: 0.82, 95% CI: 0.73, 0.93, $P = 0.003$) were associated with increased risk of death.

Conclusions. Based on our findings, most non-survivors are elderly with comorbidities. Lymphopenia and increased levels of WBCs along with elevated CRP were associated with increased risk of death. Therefore, it is best to be regularly assessed these markers during treatment of COVID-19 patients.

Key words: COVID-19, pneumonia, elderly, lymphopenia, leukocyte count, C-reactive protein, mortality.

INTRODUCTION

At the end of 2019, an acute respiratory pneumonia known as novel coronavirus infection (COVID-19) has emerged in China and rapidly spread from China to other countries [1, 2]. As of March 23, 2020, the majority of world countries (about 190 countries) were faced with the disease and at least 332,930 confirmed cases and 14,510 deaths were reported by COVID-19 worldwide [3]. To this date, Iran is ranked 6th country for both morbidity and mortality rate. Up to March 21, the number of confirmed cases in Iran has been raised to 19,664 and 1,433 death was reported. Babol in

the north of Iran was one of the first cities with confirmed cases. Babol has a population of about 530,000 which, due to the availability of appropriate hospitals and academic facilities, covers over 100,000 people of the surrounding towns for treatment during times of crisis. Despite the large outbreak over the world, the clinical symptoms and laboratory inspection of COVID-19 is largely unknown [4]. There are many symptoms of influenza, common cold, and COVID-19 that are similar, and it can be problematic to discrimination [5]. Moreover, the clinical features of severe COVID-19 patients were similar to the Middle East respiratory syndrome-related coronavirus (MERS-CoV) and severe acute

respiratory syndrome coronavirus (SARS-CoV) that might occur acute respiratory distress syndrome (ARDS), acute cardiac injury, acute liver and kidney injury and even death [6, 7]. There are no vaccines and no FDA-approved therapeutics or drugs to treat, cure or prevent COVID-19 and this issue is more important in the case of Iran, because Iran is under severe sanctions [8–10]. Despite the growing body of studies in the recent four months, there are few reports on the clinical and laboratory features of COVID-19 cases outside China, and especially in Iran. In this descriptive study we aimed to analysis the epidemiologic aspects, clinical symptoms and laboratory findings, and outcomes of the 100 patients with confirmed COVID-19 in Babol, Mazandaran province, north of Iran.

MATERIALS AND METHODS

We carried out a retrospective cohort analysis on the clinical symptoms and laboratory findings of a series of 100 confirmed adult patients (≥ 18 years old) with COVID-19. Patients were admitted to the hospitals affiliated to Babol University of Medical Sciences (Ayatollah Rohani, Shahid Beheshti and Yahyanejad hospitals) from 25 February 2020 to 12 March 2020 with final follow-up for the study on 17 March 2020. Our treatment center covers more than 1 million people living in Mazandaran province, North of Iran. To extract the clinical and laboratory data, the hospital medical records of patients were analyzed by a well-trained research team of the infectious diseases and tropical medicine research center, Babol University of medical sciences, Iran.

The following data were extracted from each medical record: epidemiological, demographic, clinical, laboratory, treatment, and outcome data. All parts of this study were approved by the Research Ethics Committee of the Babol University of Medical Science, Babol, Iran (no. IR.MUBABOL.HRI.REC.1398.350). All the enrolled patients were informed about the study. We only included physician- and laboratory-confirmed (Reverse transcription polymerase chain reaction (RT-PCR) positive) cases and suspected cases with similar clinical symptoms were excluded from this study. In other words, all adult cases who were diagnosed with COVID-19 according to the WHO interim guidance were screened, and those who were discharged or died between 25 February 2020 to 12 March 2020, were included in our study [3]. Explain further, all adults with lymphopenia (lymphocyte count $<1.0 \times 10^9/L$) and CRP elevations greater than 30 with shortness of breath and blood

oxygen saturation $<93\%$ were entered the study. All the recovered patients with COVID-19 had completely resolved signs and symptoms, had significant improvement in pulmonary (blood oxygen saturation $\geq 93\%$) and extrapulmonary organ dysfunction, and no longer needed supportive care before hospital discharge.

Methods for physician- and laboratory confirmation of COVID-19 infection have been described using the same protocols previously [11]. For example RT-PCR assessed for nasal and pharyngeal swab specimens. Also, routine blood examinations were complete blood count, coagulation profile, serum biochemical tests.

Statistical analysis

We present continuous variables as mean (SD) if they are normally distributed or median (IQR) if they are not, and categorical variables as count (%). Baseline demographic and clinical characteristics were compared among the survivor and non-survivor patients by using the independent sample t-test for continuous data and a chi-square test for categorical data. The association between these characteristics and in-hospital death was determined using univariable and multivariable modified Poisson regression. Considering the low amount of in-hospital death and to avoid overfitting in the model, only five variables (age, previous underlying diseases, comorbid conditions, CRP, Lymphocyte and WBC) were chosen for multivariable analysis. The magnitude of the effect is presented as adjusted RR and its 95% confidence interval. A two-sided α of less than 0.05 was considered statistically significant. All statistical analyses were performed with Stata 13.0 (Stata Corp LP, College Station, Texas, USA).

RESULTS

One hundred ten adult patients were hospitalized in three state hospitals with COVID-19 before 12 March 2020. One patient with a suspected diagnosis and nine inpatients without available key data in their medical records excluded. We included 100 inpatients in the final analysis. Nineteen patients died during hospitalization and 81 were discharged. The demographic and clinical characteristics are shown in Table 1. All of the 100 enrolled cases showed bilateral involvement of chest CT scans.

The mean age of the patients was 60.12 years (median: 59, IQR: 21), ranging from 18 years to 93 years, and nearly half of the patients were female.

Half of the patients (50%) had comorbidities with diabetes (34%) being the most common comorbidity, followed by hypertension (31%), coronary heart disease (22%) and Chronic kidney disease (11%). The mean interval between illness onset (hospitalization) to discharge was 7.01 (95% CI: 6.25, 7.77) days (median: 6, IQR: 6), ranging from one day to 17 days. Anorexia (86%, 95% CI: 77.62, 92.12) was the most frequently observed symptoms, followed by dry cough (82%, 95% CI: 73.05, 88.96), dyspnea

(82%, 95% CI: 73.05, 88.96), fever (77%, 95% CI: 67.51, 84.82) and fatigue (77%, 95% CI: 67.51, 84.82). Frothy three patients required mechanical ventilation, of whom 19 (44.18%, 95% CI: 29.07, 60.12) died. Acute cardiac injury (32.55%, 95% CI: 19.07, 48.54) has been the most frequently observed complication, followed by ventilator-associated pneumonia (30.23%, 95% CI: 17.18, 48.54), ARDS (9.30%, 95% CI: 2.59, 2.21) and arrhythmia (4.65%, 95% CI: 0.56, 15.81) (Table 1).

Table 1

Baseline characteristics of patients infected with COVID-19

	All patients (n = 100)	Deceased patients (n = 19)	Survivor patients (n = 81)	P-value*
Age, mean (SD), y	60.12 (13.87)	69.26 (11.10)	57.74 (13.58)	0.001
Sex				
Male	51 (51)	12 (57.1)	39 (49.4)	0.526
Female	49 (49)	9 (42.9)	40 (50.6)	
Coexisting conditions				
Hypertension	32 (32)	12 (63.15)	20 (24.69)	0.001
Diabetes	37 (37)	10 (52.63)	27 (33.33)	0.116
Malignancy	4 (4)	3 (15.78)	1 (1.23)	0.684
Cardiovascular disease	20 (20)	8 (42.10)	12 (14.81)	0.003
Chronic kidney disease	12 (12)	5 (26.31)	7 (8.64)	0.032
Liver disease	3 (3)	2 (10.52)	1 (1.23)	0.829
Cerebrovascular disease	3 (3)	2 (10.52)	1 (1.23)	0.829
COPD	12 (12)	5 (26.31)	7 (8.64)	0.032
Signs and symptoms				
Fever	77 (77)	15 (78.94)	62 (76.54)	0.823
Fatigue	77 (77)	15 (78.94)	62 (76.54)	0.823
Dry cough	82 (82)	16 (84.21)	66 (81.48)	0.780
Anorexia	86 (86)	18 (94.73)	68 (83.95)	0.223
Myalgia	50 (50)	9 (47.36)	41 (50.61)	0.798
Dyspnea	82 (82)	16 (84.21)	66 (81.48)	0.780
Expectoration	45 (45)	7 (36.84)	38 (46.91)	0.427
Pharyngalgia	26 (26)	3 (15.78)	23 (28.39)	0.259
Diarrhea	14 (14)	2 (10.52)	12 (14.81)	0.627
Constipation	16 (16)	7 (36.84)	9 (11.11)	0.005
Haemoptysis	7 (7)	1 (5.26)	6 (7.40)	0.067
Dizziness	41 (41)	10 (52.63)	31 (38.27)	0.252
Headache	59 (59)	9 (47.36)	50 (61.72)	0.897
Vomiting	45 (45)	11 (57.89)	34 (41.97)	0.209
Abdominal pain	19 (19)	3 (15.78)	16 (19.75)	0.691
Chest pain	43 (43)	12 (63.15)	31 (38.27)	0.048
Hospital admission median (IQR), d	6 (6)	5 (6)	6 (6)	0.514
Heart rate, median (range), bpm	80 (70–100)	80 (74–90)	80 (70–100)	0.769
Respiratory rate, median (range)	20 (18–24)	20 (18–20)	20 (18–24)	0.199
Mean arterial pressure, median (range), mm Hg	120.60 (90.60–160.90)	125.80 (100.60–160.90)	110.70 (90.60–150.90)	0.005
Outcome				
ARDS	4 (4)	3 (15.78)	1 (1.23)	0.003
Acute cardiac injury	14 (14)	6 (31.57)	8 (9.87)	0.014
Arrhythmia	2 (2)	1 (5.26)	1 (1.23)	0.258
Ventilator-associated pneumonia	13 (13)	6 (31.57)	7 (8.64)	0.007

Compared with survivor patients ($n = 81$), non-survivors ($n = 19$) were significantly older (MD: 11.52, 95% CI: 4.80, 18.24; $P < 0.001$) and were more likely to have underlying diseases, including hypertension (RR: 2.55, 95% CI: 1.53, 4.27; $P = 0.001$), cardiovascular disease (RR: 3.19, 95% CI: 1.51, 6.72; $P = 0.003$), chronic kidney disease (RR: 3.04, 95% CI: 1.08, 8.55; $P = 0.032$), and chronic obstructive pulmonary disease (COPD) (RR: 3.04, 95% CI: 1.08, 8.55; $P = 0.032$). The occurrence

of ARDS (3 [15.75%] vs 1 [1.23%], $P = 0.003$), Acute cardiac injury (6 [31.57%] vs 8 [9.87%], $P = 0.014$) and ventilator-associated pneumonia (6 [31.57%] vs 7 [8.64%], $P = 0.007$) was higher compared to survivor patients. Non-survivor patients had a significantly higher CRP (MD: 46.37, 95% CI: 20.84, 71.90; $P = 0.001$), WBCs (MD: 3.10, 95% CI: 1.53, 4.67; $P < 0.001$) and lower lymphocyte (MD: -8.75, 95% CI: -12.62, -4.87; $P < 0.001$) compared to survivor patients (Table 2).

Table 2

Laboratory findings of patients infected with COVID-19 on admission to hospital

	All patients ($n = 100$)	Deceased patients ($n = 19$)	Survivor patients ($n = 81$)	P-value *
White blood cell count, $\times 10^9/L$	5.70 (2.30–16.40)	8.30 (3–15.90)	5.30 (2.30–16.40)	< 0.001
Lymphocyte count, $\times 10^9/L$	2.40 (0.14–4.01)	1.45 (0.8–3.10)	2.60 (0.14–4.01)	< 0.001
Eosinophils count, $\times 10^9/L$	3 (1–10)	2.50 (1–10)	3 (1–8)	0.598
Platelet count, $\times 10^9/L$	186 (90–436)	210 (90–421)	183.5 (90–436)	0.062
Creatinine, $\mu\text{mol/L}$	100 (60–530)	110 (70–380)	100 (60–530)	0.102
C-reactive protein (mg/L)	52 (1.9–243)	92 (12–243)	47.15 (1.9–174)	0.001
Haemoglobin (g/L)	12.2 (6.1–16)	12.15 (9.5–14.6)	12.20 (6.1–16)	0.761
Potassium (mmol/L)	4.17 (3.4–5.2)	4.20 (3.7–5)	4.10 (3.4–5.2)	0.121
Sodium (mmol/L)	135 (117–145)	133 (117–145)	135 (128–145)	0.001

The area under the ROC curve for CRP levels as a predictor of in-hospital death was 70.70 (95% CI: 56.50, 84.89). A CRP level of >64.8 mg/dl associated with in-hospital death, with a sensitivity of 70.05% (95% CI: 60.01, 78.75), the specificity was 70.59% (95% CI: 62.10, 79.89), the positive LR was 2.38, and the negative LR was 0.42. A WBC of >6.9 count $\times 10^9/L$ (AUC: 74.68, 95% CI: 61.79, 87.57) and a lymphocyte of >1.7 count $\times 10^9/L$ (AUC: 79.71, 95% CI: 69.04, 90.37) were associated with infection, with a sensitivity of 73.68% and 84.62%, and a specificity of 67.09% and 65.0%, respectively (Figure 1). We found that comorbid conditions (aRR: 2.99, 95% CI: 1.09, 8.21, $P = 0.034$), higher CRP levels (aRR: 1.02, 95% CI: 1.01, 1.03, $P = 0.044$), and lower lymphocyte (aRR: 0.82, 95% CI: 0.73, 0.93, $P = 0.003$) were associated with increased risk of death.

Figure 1. Receiver operating characteristics curves of (A) C-reactive protein, (B) white blood cell, and (C) Lymphocyte in the prediction of in-hospital death.

All 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 with Kaletra (lopinavir/ritonavir) two 200 mg tablets BID, for 5–14 days. Moreover, cephalosporins and glycopeptide antibiotics have also been used for some patients with suspected staphylococcal infections.

DISCUSSION

COVID-19 is mainly transmitted through respiratory droplets and also close contact with infected cases, and the studies into the viability of the virus outside the body have not yielded any accurate results [12]. The clinical course of COVID-19 was characterized by fever, mostly dry cough, and the development of gradual dyspnea in some cases and also ARDS in severe patients [13].

The current retrospective cohort study identified some risk factors for death in 100 adult cases who were admitted to the hospitals affiliated to Babol University of Medical Sciences with COVID-19 for the first time. In particular, older age, underlying diseases, elevated levels of CRP, WBCs and lymphopenia on admission were associated with higher odds of death in the hospital.

In agreement with the results of our study, other researchers showed that sex may not be an influencing factor of disease-related mortality of COVID-19. These results differ from some other reports that showed COVID-19 is more likely to affect males [14].

Advanced age was a risk factor for viral infection and poor prognosis. Our data suggested that deceased patients were older than survived cases. In agreement with our study Wang et al. suggested that age and comorbidity can be risk factors for poor outcomes [12]. The possible reason for the association between infection-related mortality, particularly viral infections with age, may be due to impaired cellular immune function and a longer duration of inflammation in the elderly [15].

As reported in previous studies, patients who have a history of coexisting conditions as hypertension, diabetes, cardiovascular disease and malignancies are at higher risk of COVID-19 infection [16]. Recent studies revealed that the majority of coronavirus cases were patients with chronic diseases, which indicated that these patients might also be at increased risk of becoming critically ill or death [17]. Our study showed that non-survivors were significantly more likely to have underlying diseases, including hypertension, cardiovascular disease, chronic kidney disease, and COPD.

Our research showed that lymphopenia occurred in many patients particularly non-survivors, which is a key laboratory feature in COVID-19 cases. Studies reported that more than 80% of critically ill patients with COVID-19 showed lymphopenia [18]. It is important to note lymphopenia as a trace of severe COVID-19 was confirmed by some researchers who revealed that deceased cases exhibiting significant lymphopenia. Studies revealed that endothelial dysfunction following chronic conditions induces some defects as endothelial cell death, enhanced leukocyte extravasation, and blood-tissue barrier disruption which might contribute to describe the lymphopenia detected in severe COVID-19 cases [19].

We also found that elevated initial CRP was a factor associated with death in COVID-19 patients. Our study reported that CRP levels of >64.8 mg/dl associated with in-hospital death, sensitivity and specificity of 70.05% and 70.59%, respectively.

As studies have shown CRP is one of the most sensitive acute-phase reactants and is almost absent in healthy individuals. CRP levels can increase after viral and bacterial infections, and inflammations [20]. CRP is an important marker of inflammation but lacks the required specificity for differentiation between bacterial and viral infections. Our laboratory results showed that the WBCs and CRP levels were elevated in non-survivors and the lymphocytes were decreased.

Based on these results it can be suggested that severe pneumonia in COVID-19 may be accompanying bacterial infection and also immune deficiency in the elderly may be an influencing factor for poor prognosis in these cases [21]. Therefore, elevated CRP and WBCs level along with lymphopenia reflects their role in the pathogenesis of COVID-19 and also particularly CRP and lymphopenia may serve as an important predictor of COVID-19 mortality.

Our study has some limitations. First, due to the critical condition caused by this infection, the sample size of the report has decreased at this point. Therefore, it is advisable to use more sample sizes in subsequent studies to more accurately assess the association between variables. Second, due to the retrospective study design, not all laboratory tests were done in all patients.

CONCLUSION

Most non-survivors were older patients with comorbidities (especially hypertension, cardiovascular disease, chronic kidney disease, and COPD).

Gradually decreased lymphocytes and increased WBCs along with inflammation biomarkers as CRP were associated with increased risk of death. Thus,

it is suggested that clinicians evaluate these factors in the initial diagnosis of this infection and also during the treatment of the infection.

Introducere. În decembrie 2019 în China a apărut o epidemie cu noul coronavirus (COVID-19), patologie ce s-a răspândit pe toate continentele. Scopul studiului a fost de a evalua caracteristicile clinice și paraclinice ale infecției cu noul virus.

Materiale și metode. A fost realizat un studiu retrospectiv pe 100 de pacienți cu COVID-19. Pacienții au fost internați în spitalele afiliate Universității din Babol din 25 februarie 2020 până pe 12 martie 2020.

Rezultate. 19 pacienți au decedat și 81 au fost externați. Pacienții non-supraviețuitori au avut niveluri mai mari ale proteinei C reactive-CRP (MD: 46,37, 95% CI: 20,84, 71,90; $P = 0,001$), leucocitoza (MD: 3,10, 95% CI: 1,53, 4,67; $P < 0,001$) și limfocite mai puține (MD: -8,75, 95% CI: -12,62, -4,87; $P < 0,001$). Comorbiditățile aRR: 2,99, 95% CI: 1,09, 8,21, $P = 0,034$), niveluri crescute ale CRP (aRR: 1,02, 95% CI: 1,01, 1,03, $P = 0,044$) și prezența limfopeniei (aRR: 0,82, 95% CI: 0,73, 0,93, $P = 0,003$) s-au asociat cu riscul de deces.

Concluzii. Prezența comorbidităților, a limfopeniei și niveluri mai mari ale CRP s-au asociat cu un risc mai mare a mortalității. Așadar acești biomarkeri sunt de analizat în timpul tratamentului pacienților cu COVID-19.

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