Journal of Acute Disease

Original Article

doi: 10.4103/2221-6189.307390 jadweb.org

Chest radiography findings and hematological values: Early findings on COVID−19 patients from Turkey

Fatih Uzer[1], Begum Uzer[2], Fatma Mutlu Kukul Guven[2], Idris Kirhan[3], Nilay Coplu[4]

[1]*Kastamonu State Hospital, Pulmonology, Kastamonu, Turkey*

[2]*Kastamonu State Hospital, Emergency Medicine, Kastamonu Turkey*

[3]*Harran University Faculty of Medicine, Internal Medicine Department, Şanlıurfa, Turkey*

[4]*Kastamonu University Faculty of Medicine, Department of Microbiology, Kastamonu, Turkey*

ABSTRACT

Objective: To investigate the chest radiography findings, hematological values and the risk factors of the mortality of coronavirus disease 2019 (COVID-19).

Methods: Patients who were diagnosed with COVID-19 in a secondary-level state hospital in Turkey from March to April 2020 were included in the study. COVID-19 diagnosis was confirmed by reverse transcriptase-polymerase chain reaction. Initial routine blood tests and chest radiography findings were examined. The relationship between chest radiography findings and hematological values and risk factors of the mortality of COVID-19 were assessed.

Results: In total, 94 patients with confirmed COVID-19 diagnosis were included in the study. Among them, 33 patients did not have lung involvement (RALE score of 0), and 42 had moderate lung involvement (RALE score of 1 to 4), and 19 had severe lung involvement (RALE score of 5 to 8). Patients with higher RALE scores were significantly elder (P=0.000) and had significantly lower lymphocyte count (P=0.032). Patients in need of intensive care had a lower mean number of platelets compared to patients who did not require intensive care (P=0.007). The receiver operating characteristic analysis revealed that RALE score (P=0.005), age (P=0.002), duration of symptoms (P=0.006), neutrophil-lymphocyte ratio (P=0.007), and lymphocyte percentage (P=0.012) were significantly associated with the risk of mortality.

Conclusions: Patients with severe lung involvement have lower lymphocyte values and ratios. Age, RALE score, duration of symptoms, neutrophils/lymphocytes ratio, lymphocytes percentage are risk factors of mortality of COVID-19.

KEYWORDS: COVID-19; Chest X-ray; Survey; Lymphocyte

1. Introduction

In late 2019, the coronavirus disease (COVID-19) outbreak occurred initially as an infection of an unknown cause. In March 2020, COVID-19 was declared as a global pandemic by the World Health Organisation (WHO)[1] and has been affecting millions of people around the world. The common symptoms of the disease include fever, myalgia, respiratory and gastrointestinal complaints. Although COVID-19 infections are frequently self-healing, it can lead to serious outcomes including metabolic acidosis, septic shock, coagulopathy, acute respiratory distress syndrome[1-3], and fatality, particularly in patients of advanced age or with comorbid diseases[4].

In many hospitals, first-line investigatory tests for patients admitted with suspected COVID-19 include radiographic imaging, such as chest radiography or computed thorax tomography, and blood routine tests, such as a complete blood count, coagulation tests, acute phase reactant tests, blood gases, and serum biochemical tests (liver function tests, kidney function tests, electrolytes, *etc.*). These first-line investigatory tests are accessible, low-cost, and easy to evaluate, and they may provide important information regarding

✉To whom correspondence may be addressed. E-mail: uzerfatih@gmail.com

How to cite this article: Uzer F, Uzer B, Guven FMK, Kirhan I, Coplu N. Chest radiography findings and hematological values: Early findings on COVID-19 patients from Turkey. J Acute Dis 2021; 10(1): 17-22.

Article history: Received 12 August 2020; Revision 1 January 2021; Accepted 13 Janaury 2020; Available online 25 January 2021

prognosis. Blood routine tests and chest X-ray findings have been reported to be associated with prognosis[1,3], while reduced count and percentage of lymphocyte may indicate a poor prognosis[3]. However, definitive evidence is lacking regarding which markers are most predictive of the severity, therapeutic response, or prognosis. In this study, we investigated the relationship between chest radiography findings and hematological values of COVID-19 patients, and risk factors of the mortality of COVID-19.

2. Materials and methods

2.1. Ethical approval

This is an observational study. Ethical committee approval was obtained from Harran University Faculty of Medicine (Approval number: HRU/20.09.18).

2.2. Patients

Patients who were diagnosed as COVID-19 in a secondary-level state hospital in Turkey from March to April 2020 were included in the study. COVID-19 diagnosis was confirmed by the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in nasal, oral, or sputum specimens using real-time reverse transcriptase-polymerase chain reaction (rRT-PCR). Initial blood routine tests and chest radiography were performed. Patients' data were recorded in a data collection form. These data included socio-demographic data, clinical tests results, history of contact with a person with COVID-19, and whether or not the patient met the Turkish Ministry of Health (MOH) criteria of COVID-19. The MOH defined COVID-19 according to the following standards: (1) has fever and respiratory symptoms and either a history of being abroad or contacts with relatives who have a history of being abroad within 14 days prior to the onset of symptoms; (2) at least has one of the symptoms of fever or respiratory symptoms and close contacts with a verified COVID-19 case within 14 days prior to the onset of symptoms; (3) has fever and severe respiratory failure requiring hospitalization without other obvious cause; (4) has abrupt onset of fever accompanied by cough or shortness of breath without nasal discharge[5].

2.3. Imaging

Chest radiographs taken at the time of admission or after admission for the first time during the patient's stay were evaluated by a pulmonologist and two emergency medicine specialists. Inter-rater agreement between the evaluators was 95.7%. Radiographic features were observed following the Fleischner guidelines, such as infiltration, ground glass, effusion, and nodule[6]. Radiographic distributions include peripheral, central; upper, middle, lower lobe, and lingula; left, right, and bilateral. To define the extent of the infection, a simple version of the Radiographic Assessment of Lung Edema (RALE) score[7] was used. Following the RALE scoring criteria, ground glass and infiltration areas seen in each lung were assigned a score ranging from 0 to 4 points (0: none, 1: <25% of lung, 2: 25% to 50% of lung, 3: 50% to 75% of lung, 4: >75% of the lung) (Figure 1). The scores for each lung were added up; thus patients could be assigned a minimum of 0 and a maximum of 8 points.

2.4. Laboratory confirmation of COVID–19

Oral and nasopharyngeal specimens were taken by a doctor at the

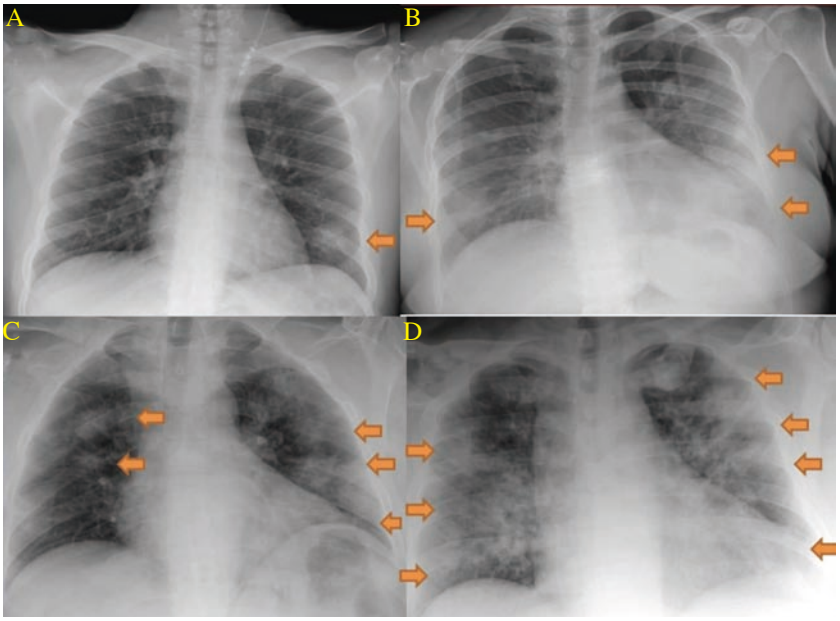

Figure 1. Chest X-ray scoring system. Examples of chest X-ray severity scores in patients with COVD-19 (right lung scores + left lung scores = total scores, one yellow arrow refers to 1 point): A: 0+1=1. B: 1+2=3. C: 2+3=5. D: 3+4=7.

time of admission and at multiple time points during the hospital stay. Specimens from patients who met the MOH definition of COVID-19 were examined in the microbiology laboratory of Kastamonu Training and Research Hospital and verified by the Public Health Headquarters. Verification of COVID-19 cases was conducted using nucleic acid amplification tests for SARS-CoV-2 and rRT-PCR. When necessary, specific sequences of viral RNA were identified and verified by nucleic acid sequence analysis. RNA extraction was performed in a BSL-2 or equivalent biosafety cabinet. Patients with a positive rRT-PCR test result were considered as confirmed COVID-19 cases. If a patient was suspected of having COVID-19 according to the clinical and radiological criteria but had a negative rRT-PCR result, then the test was repeated.

2.5. Statistical method

Data were analyzed using SPSS for Windows version 22.0 software (Statistical Package for Social Science, Chicago, II, USA). Means, standard errors (SD), frequency, and percentages were used to describe participants' characteristics. The normality of distribution was confirmed by the Shapiro-Wilk's W-test. Variables with a normal distribution were expressed as mean ± SD and compared using Student's *t*-test. Variables with a non-normal distribution were described as median and interquartile range (IQR), and analyzed by non-parametric tests. A Receiver Operating Characteristic (ROC) analysis was conducted to identify predictive factors of mortality risk. ROC curves were generated for different prognostic factors. Area Under the Curve (AUC) values were used to compare the ROC areas. The significance level of this study was set at α=0.05.

3. Results

In total, 94 patients with confirmed COVID-19 diagnosis were included in the study, including 51 (54.3%) male patients and 43 (45.7%) female patients. The patients' age ranged from 3 to 88 years, with a mean age of (51.9±19.7) years (Table 1). In total, 16 (17%) patients were asymptomatic. Among the patients with symptoms, the commonest complaints were cough, fever, and shortness of breath. The duration from exposure to onset of symptoms was 5 (1-20) d; the duration of hospitalization was 12 (1-35) d. Chest radiography findings included the following: ground-glass appearance (n=41, 43.6%), normal lung appearance (n=33, 35.1%), consolidation (n=17, 18.1%), atelectasis (n=2, 2.1%), and pleural effusion (n=2, 2.1%). Computed tomography revealed that the most prevalent pattern of respiratory involvement was bilateral lung involvement affecting the inferior lobes, and the least involved lung segment was the lingula. In total, 33 patients did not have lung involvement (RALE score of 0), 42 had moderate lung involvement (RALE score of 1 to 4), and 19 had severe lung involvement (RALE score of 5 to 8).

According to the MOH definition of COVID-19, 30 (31.9%) patients matched category A, 35 (37.2%) matched category B, 6 (6.4%) matched category C, and 23 (24.5%) matched category D. In total, 31 (33.0%) patients had a comorbid disease; the most frequent comorbid diseases identified were hypertension (14.9%), diabetes mellitus (11.7%), and chronic obstructive lung disease (7.4%). Patients with higher RALE scores were significantly elder (P=0.000) and had significantly lower lymphocyte count (P=0.032) and longer hospital stay (P=0.000) (Table 2). In total, 10 patients required intensive care, among whom 6 patients had at least one comorbid disease and 2 cases resulted in death. Patients in need of intensive care had a longer mean duration of hospitalization (P=0.001) and a lower mean number of platelets (P=0.007) compared to patients who did not require intensive care. No other parameters were found to be significantly different between the patients who needed and did not need intensive care (Table 3). We found that lymphocyte counts were slightly lower among patients with a hospital stay of more than 14 d compared to patients with a stay of 14 d or fewer, but this finding was not statistically significant (P=0.650) (Table 4).

The ROC analysis revealed that RALE score (P=0.005), age (P=0.002), duration of symptoms (P=0.006), neutrophil-lymphocyte ratio (P=0.007), and lymphocyte percentage (P=0.012) were significantly associated with risk of mortality (Table 5).

Table 1. Characteristics of the study patients.

Variables	*N*	%
Gender		
Female	43	45.7
Male	51	54.3
Need for intensive care unit		
Yes	10	10.6
No	84	89.4
Computed thorax tomography		
Only right lung involvement	10	10.6
Only left lung involvement	5	5.3
Bilateral	49	52.1
Central	11	11.7
Peripheral	62	66.0
Superior lobe	33	35.1
Lingula	12	12.7
Right middle lob	35	37.2
Inferior lobe	57	60.6
Chest radiography		
Normal	33	35.1
Ground-glass	41	43.6
Consolidation	17	18.1
Atelectasis	2	2.1
Pleural effusion	2	2.1
Complaints		
Fever	21	22.3
Cough	26	27.6
Myalgia	11	11.7
Dyspnea	13	13.8
Sore throat	5	5.3
Gastrointestinal complaints	1	1.1
Anosmia	1	1.1
Asymptomatic	16	17.0

Table 2. Comparison according to the RALE scores.

Variables	0	1-4	5-8	*F*	*P*-value
Age (years) (mean±SD)	39.8±17.2	55.6±19.4	65.1±11.8	14.450	<0.001
Fever (Celsius) [median (IQR)]	36.7 (1.5)	38.0 (2.1)	36.2 (2.3)	1.479	0.246
Duration of hospitalization (d) [median (IQR)]	9.0 (4.2)	13.0 (4.2)	22.1 (4.0)	8.549	<0.001
Leukocytes/μL [median (IQR)]	5380.0 (2685.0)	5400.0 (2570.0)	5100.0 (3890.0)	0.536	0.587
Neutrophils/μL [median (IQR)]	2910.0 (2310)	3690.0 (1977.5)	3620.0 (3690.0)	2.679	0.074
Lymphocytes/μL [median (IQR)]	1430.0 (1105.0)	1290.0 (812.5)	1010.0 (650.0)	3.577	0.032
Lymphocyte precentage [median (IQR)]	30.7 (19.8)	25.6 (13.9)	18.6 (10.2)	10.232	<0.001
Platelet/μL [median (IQR)]	214000.0 (68000.0)	177000.0 (81500.0)	200000.0 (97000.0)	2.001	0.141
Lactate (mmol/L) [median (IQR)]	1.6 (0.7)	1.6 (0.7)	1.6 (0.6)	0.043	0.958

Table 3. Comparison between patients with or without need of intensive care.

Variables	No need for intensive care	Need for intensive care	*t*/*Z*	*P*-value
Age (years) (mean±SD)	51.2±10.0	57.9±13.6	–1.002	0.057
Duration of hospitalization (d) [median (IQR)]	12.00 (5.70)	16.50 (17.50)	–2.389	0.001
Leukocytes/μL [median (IQR)]	5360.00 (9470.00)	5235.00 (2670.00)	–0.411	0.681
Neutrophils/μL [median (IQR)]	3500.00 (2170.00)	3405.00 (1090.00)	–0.110	0.912
Neutrophils/lymphocytes [median (IQR)]	2.60 (2.40)	2.20 (2.40)	–0.174	0.613
Lymphocytes/μL [median (IQR)]	1260.00 (1050.00)	1455.00 (942.50)	0.516	0.378
Lymphocyte percentage [median (IQR)]	25.10 (15.80)	25.90 (15.00)	–0.273	0.609
Platelet/μL [median (IQR)]	202000.0 0 (89000.00)	134500.00 (94000.00)	2.644	0.007
Lactate (mmol/L) [median (IQR)]	1.60 (0.60)	1.60 (0.85)	0.502	0.655

Table 4. Comparison of patients according to the duration of hospitalization.

Variables	⩽14 d	>14 d	*t*/*Z*	*P*–valve
Age (years) (mean±sd)	49.2±21.3	61.3±11.7	–2.700	0.001
Fever (Celsius) (mean±SD)	37.2±1.0	37.8±0.9	–1.332	0.009
Leukocytes/μL [median (IQR)]	5400.00 (2735.00)	5185.00 (1890.00)	–0.045	0.922
Neutrophils/μL [median (IQR)]	3515.00 (2307.50)	3460.00 (1442.50)	–0.450	0.931
Lymphocytes/μL [median (IQR)]	1245.00 (1097.50)	1210.00 (705.00)	–0.401	0.650
Neutrophils/lymphocytes [median (IQR)]	2.60 (2.90)	2.50 (1.50)	–1.251	0.776
Lymphocyte percentage [median (IQR)]	25.10 (67.90)	23.30 (36.62)	–1.110	0.117
Platelet/μL [median (IQR)]	197000.00 (91500.00)	199000.00 (99750.00)	–0.579	0.756
Lactate (mmol/L) [median (IQR)]	1.50 (0.60)	1.70 (0.70)	–1.209	1.000

Table 5. The ROC analysis of mortality.

Risk factors	AUC (95%CI)	Cutoff	*P*-value	Sensitivity (%)	Specificity (%)
Age (years)	0.787 (0.613-0.961)	66.000	0.002	75.0	69.2
RALE scores	0.913 (0.804-1.000)	5.500	0.005	75.0	89.8
Durations of symptoms (d)	0.712 (0.559-0.818)	7.000	0.006	100.0	57.6
Hemoglobin	0.408 (0.218-0.597)	13.100	0.534	55.7	44.3
Leukocytes/μL	0.563 (0.140-0.985)	5355.000	0.674	50.0	50.0
Neutrophils/μL	0.690 (0.392-0.989)	3465.000	0.200	50.0	50.0
Lymphocytes/μL	0.349 (0.014-0.685)	1255.000	0.310	50.0	50.0
Neutrophils/lymphocytes	0.903 (0.827-0.980)	4.800	0.007	100.0	81.8
Lymphocyte percentage	0.126 (0.047-0.206)	15.450	0.012	25.0	19.5
Platelet/μL	0.534 (0.312-0.756)	209000.000	0.818	50.0	58.0
D-dimer	0.608 (0.361-0.808)	0.565	0.126	50.0	52.3

4. Discussion

In this study, we evaluated 94 hospitalized patients with a COVID-19 diagnosis confirmed by rRT-PCR. We found that patients with higher RALE scores had lower lymphocyte count and percentage and patients who needed intensive care had significantly lower platelet values.

Among hospitalized patients, males comprised a higher proportion of confirmed COVID-19 cases than females. Our finding that 54% of patients with confirmed COVID-19 were male is consistent with the studies on COVID-19 from China, which reported that 54% to 73% of patients were male[2,4,8]. SARS-CoV, MERS-CoV, and other coronaviruses associated with large outbreaks and high mortality have also been reported to be more prevalent in males than in females[9,10]. Gender differences in innate and adaptive immune responses, which may be linked to the X chromosome and female hormones[11], may play an important role in the apparent greater susceptibility of male to COVID-19 disease.

COVID-19 appears to be more infectious among adults compared with children[12]. Several studies have shown that children younger than 18 years comprised less than 1% of COVID-19 cases in Italy, 3% to 4% of cases in China, and 5% of cases in the USA[13-15]. Similarly, our study showed that only 3 (3.1%) were younger than 18 years, while most were 65 years or older. This pattern may be attributed to the decreased immunity in older individuals, as well as to waning immune memory to childhood Bacillus Calmette-Guérin (BCG) vaccination after the age of 30[16]. In countries such as Turkey, where children are routinely vaccinated with BCG, adult COVID-19 infection is milder than in countries without routine BCG vaccination. All in all, COVID-19 is also less common in children, which may be a result of improved cellular immunity following BCG vaccination[17-19].

The most common symptoms of COVID-19 reported in the literature are fever, cough, and shortness of breath, and only a small percentage of cases are reported to be asymptomatic[2,4,8,12,13]. Similarly, in our study, we found that the most common symptoms were fever, cough, and shortness of breath, and patients rarely had gastrointestinal symptoms or anosmia. As with symptoms, the mean incubation period observed (6.2 d) in our study was similar to that reported in other clinical studies of COVID-19 (2-14 d) [4,8,12]. However, in contrast to other reports[2,4,8,12], we found a considerable proportion of asymptomatic cases. This difference may be due to differences between the Turkish Ministry of Health definition of COVID-19 and that used by other countries.

In December, 2020, according to official records, the mortality rate of COVID-19 in Turkey was 0.9%, while the rate of COVID-19 patients requiring intensive care was 4.3%[20]. In studies from China, mortality rates ranged from 0.9% to 4.3%, while the rate of patients requiring intensive care ranged from 5% to 32%[4,8,13,21,22]. In our study, the mortality rate was 2.1%, while the rate of patients needing intensive care was 9.4%. Wang *et al.* reported that COVID-19 patients needing intensive care had lower lymphocyte counts, lower lymphocyte ratios, and increased values of urea, creatinine, and lactate dehydrogenase. The authors interpreted these biomarker patterns as evidence of disrupted cellular immunity[4]. Similarly, a study by Guan *et al.* reported that lymphocytopenia and leukopenia are common among severe COVID-19 cases[22]. Our study broadly agrees with these findings. We found that patients requiring intensive care had significantly lower platelet counts, but no other significant difference in biomarkers was noted. We also found that lymphocyte counts and ratios were lower in patients with more extensive lung involvement.

COVID-19 has been reported to have a greater effect on elderly people and those with comorbid diseases. Graselli *et al.* reported that, in Italy, among the patients diagnosed with COVID-19, 68% had at least one comorbid disease, and all patients over the age of 80 had at least one comorbid disease[23]. In studies from China, the proportion of patients with a comorbid disease ranged from 23.7% to 58.3%[4,22,24]. In all studies we found, the most frequently reported comorbid disease is hypertension. The profile of comorbid disease among COVID-19 patients in our study was similar to that reported in the studies from China[4,22,24]. In our study, 33% of the patients had at least one comorbid disease, and the most common comorbid condition was hypertension.

Our study had several limitations that should be considered when interpreting the results. We reported a low number of cases requiring intensive care and having a mortal course, which may have been due to our use of rRT-PCR for confirmation of COVID-19 diagnosis. Thus we excluded patients with negative COVID-19 rRT-PCR results, who may nevertheless have been infected since they had clinical and imaging results consistent with COVID-19.

In conclusion, this study reported on the very first cases of COVID-19 in Turkey, finding that COVID-19 infection had the greatest impact on males and elderly individuals, and primarily presents with fever and cough. Patients with higher RALE scores had lower lymphocyte count and percentage. Compared to other patients, those requiring intensive care had significantly lower platelet counts; intensive care patients also had lower lymphocyte counts and ratios, but the difference is insignificant.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

F.U. and B.U.: study design, data collection, data analysis, and manuscript preparation, and final edition. F.M.K.G., I.K., N.C. had role in manuscript preparation and data analysis.

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