# Are Patients with Elevated Inflammatory Indications are at Higher Risk for Developing the Severe form of COVID-19?

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# Abstract

Background

Since December 2019, when SARS-CoV-2 emerged with a cluster of unknown pneumonia cases in Wuhan city and rapidly spread throughout in worldwide and Iran, data have been needed on the clinical and diagnostic features of the affected Iranian patients.

Methods

We extracted data regarding 233 patients with laboratory-confirmed COVID-19 from Buali Hospital in Iran; clinical/praclinical and inflammatory indexes data were collected and analyzed. The data of laboratory examinations and chest CT findings were compared between death and non-severe patients.

Results

The mean age of the patients was 49 years, (63%) of the patients were male. The acute respiratory distress syndrome occurred in 64 patients, including 53 who were admitted to the ICU and underwent invasive mechanical ventilation, and 28 who died. On the admission in death group, lymphopenia (79%), neutrophilia (79%), and thrombocytopenia (21%) were usually observed. Most patients had a high SII index of > 500 (68%), increased CRP level (88%). A high level of inflammatory index's such as NLR, PLR and SII in death comparison with moderate groups were observed ($P < 0.001$). The most common symptoms were fever (70%) and cough (63%) on admission. Headache was uncommon (11%). On admission, ground-glass opacity with consolidation (mixed) was the most common radiologic finding on chest CT (51%). No radiographic or CT abnormality was found in 15 of 204 patients (7%).

In Conclusion

These patients often presented without fever, and some did not have abnormal radiologic findings. Elevated NLR, PLR and SII can be considered as prognostic and risk stratifying factor of severe form of disease.


# Background

In late December 2019, a cluster of unknown pneumonia cases has been reported in Wuhan, China. A few days later, the causative agent of this mysterious pneumonia was recognized as a new coronavirus. This causative virus has been temporarily named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the relevant infected disease has been named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) [1, 2]. At present, the cases of COVID-19 have been found in many countries around the world such as USA, Italia, Spain and etc. According to the latest data, up to the May 24, 2020, the number of laboratory-confirmed cases in Iran reached 135,701 of which 7,417 were dead, and 104,072 were cured also 2,513 were severe illness. In addition to Iran, the number of laboratory-confirmed cases in other countries also reached 5,304,772 of which 342,029 were dead, and 1,184,459 were cured according to official data from the WHO.

Many medical studies have shown that COVID-19 patients have obvious inflammatory responses, accompanied by a decrease in the absolute count of lymphocytes in the peripheral blood circulation and an enhancement in the number of neutrophil [3]. Most patients with SARS-CoV-2 infection were mild/moderate that are characterized by fever, malaise, cough, upper respiratory symptoms, and/or less common features of COVID-19, in the absence of dyspnea. Most of these patients do not need hospitalization [4]. However, nearly 15–20% of cases would develop severe illness, which has laboratory risk factors for disease progression. Some of these patients need hospitalization in intensive care unit (ICU) [5, 6]. Organ dysfunction including acute respiratory distress syndrome (ARDS), shock, acute cardiac injury, and acute renal injury, can happen in 5% of severe cases with COVID-19 [4, 7]. Since most COVID-19 infected patients were detected with pneumonia and feature computed tomography (CT) scan imaging patterns, radiological (X ray) examinations have become vital diagnostic method in early detection's and assessment of ill course [8]. Typical chest CT scan findings of COVID-19 include peripherally distributed multifocal ground-glass opacities (GGOs) with patchy consolidations and posterior part or lower lobe involvement predilection. Increasing numbers, extent and density of GGOs on CT scan indicate disease progression [7, 9]. These pathological damages might be attributable to indirect cytokines release syndrome (CRS) e.g. interleukin (IL)-1, IL-6 and TNF-α initiated by immune system and direct attack from SARS-CoV-2 [10].

In this study, we compared the clinical/diagnostic features, imaging manifestation and outcomes of disease in mild/moderate illness and severe (as result some death) COVID-19 patients, to discover the useful prognostic index for an accurate individualized assessment of the COVID-19 severity.

## Methods

# Design and Participants

This case-control study was performed in referral hospital for COVID-19 patients in Zahedan, Iran. Participants included 233 hospitalized patients with confirmed COVID-19 infection in our hospital from February 29, 2020 to May 24, 2020. The protocol of the present study was approved by the ethical committee of ZAUMS, and written consent was obtained from the patients or their guardians. The clinical classifications in this study are as follows, mild/moderate: with the respiratory distress and means oxygen saturation ≤ 93%; severe with one of the following conditions: respiratory failure occurs and requires mechanical ventilation, shock occurs or ICU admission is required for combined organ failure.

# Data collection

From all suspected patients for SARS-CoV-2 infection that were admitted to the hospital for hospitalization in infectious unit, oro- and naso-pharyngeal swab spacemen were taken and stored in VTM medium (virus transport medium) and the confirmed diagnosis of SARS-CoV-2 was defined as a positive result of real time reverse transcriptase polymerase chain reaction (RT-PCR). In addition fasting venous blood were collected for paraclinical assessment.

All of the patients, routine blood biochemistry parameters, complete cell blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and chest radiological/CT scan were performed. Routine blood biochemistry analyses included liver function test (LFT), renal function, electrolytes test, lactate

dehydrogenase (LDH), myocardial enzymes e.g. creatine phosphokinase (CPK), D-Dimer and status of other virus infection.

# Real-Time Reverse Transcription Polymerase Chain Reaction Assay

Viral ribonucleic acid was extracted from the oro- and naso-pharyngeal swab samples using the COVID-19 ORF1ab/N gene nucleic acid detection kit (manual). The sequences were as follows: forward primer 5'-TCAGAATGCCAATCTCCCCAAC-3'; reverse primer 5' AAAGGTCCACCCGATACATTGA-3'; and the probe 5'CY5-CTAGTTACACTAGCCATCCTTACTGC-3' BHQ1. Also the reaction procedure were as follows: 50 °C for 30 min, pre-denaturation at 95 °C for 10 min, followed by 5 cycles of 94 °C for 15 s, 50 °C for 30 s and 72 °C for 30 s, and 40 cycles of 94 °C for 10 s and 58 °C for 30 s for fluoresce detection. According to the cycle threshold (Ct) analysis, if the Ct values of the fluorescein amidites (FAM) channel and victoria (VIC) channel are ≤ 37, and the curve is S-shaped with a significant exponential growth period, the test result specimen is positive, if the Ct value of one channel is ≤ 37, the specimen should be tested again. If the Ct values of both channels are > 37, and the internal standard channel test result is positive, then the test result specimen is negative.

# Inflammatory indications

Inflammation index were detected using specific parameters of blood analysis. These indexes were as follows: neutrophil to lymphocyte ratio (NLR) by dividing the neutrophil absolute count to the lymphocyte absolute count and platelet to lymphocyte ratio (PLR) by dividing the platelet count to the lymphocyte absolute count were defined. Systematic immune-inflammation index (SII) was calculated base on as platelet count multiplied NLR (per μL).

# Statistics analysis

All of the data presented by mean ± standard error of mean (SEM). Analysis was performed with the IBM SPSS version 23.0 statistical software package, with an independent sample t test for comparison between groups. Descriptive statistics were performed to determine the patient's diagnostic and clinical features. *P*-Value less than 0.05 was indicated statistically significant.

## Results

A total of 1,911 patients with a mild/moderate or severe symptoms of COVID-19 during 3 month were admitted in our hospital, of these cases, 233 patients with confirmed diagnosis of COVID-19 with RT-PCR method. About 12% (28/233) of patients with confirmed diagnosis of this disease were dead. In the same time, the rate of mortality for all causes in this hospital was 2.04% (39/1911). Of the 233 patients with SARS-CoV-2 infection included in this study, 205 were diagnosed as mild/moderate or severe (hospitalized group) and 28 were as severe on admission in hospital and expire (death group, [see Table 1]). The mean age of two groups, respectively hospitalized group and death group (47.6 versus 65.3 year old), was statistically significant different ($P < 0.0001$). Most of the death cases (71.4%) and hospitalized cases )62.9%) were male.

Table 1
Demographic features of all patients with and without COVID-19

| **Clinical features patients COVID-19 Stat** | | **N = 233** |
|---|---|---|
| Age, years | 16–40 Y | 77 (33.1%) |
| | 40–60 Y | 84 (36.1%) |
| | > 60 Y | 72 (30.8%) |
| Gender | Male | 129 (62.9%) |
| | Female | 76 (37.1%) |
| Expire | ICU | 28 (12%) |
| Intubation | EMS | 20 (8.6%) |
| Recharge | | 12 (5.2%) |
| | | 201 (86.3%) |
| Severe Pneumonia | | 44 (18.9%) |
| Mild/Moderate Pneumonia | | 189 (81.1%) |
| **Total Patients Referred** | Transfer to ICU | 1911 |
| Total Hospitalization | | 629 |
| | | 53 |
| Total RT-PCR Test | Positive RT-PCR | 1259 |
| | | 233 |
| Chest CT-SCAN | | 3266 |
| **Follow up** | Recurrence after recovery | 7 |
| | Death after Recharge | 2 |

# Clinical and laboratory findings

As indicated in Table 2, on the admission, fever < 38°c (70%) and dry cough (63%) were the main common symptoms. In addition, dyspnea (62%), $SPO_2$ <%93 (55%) and muscle or chest pain (32% / 22%) were observed in patients. In the death groups, most of the infected patients were men (twenty, 71%); more than half had underlying diseases (sixteen, 64%), including hypertension (seven, 25%), diabetes (six, 21%), and cardiovascular disease (three, 11% [Table 3]).

Table 2
Signs and symptoms at admission of overall 233 COVID-19 patients

| Signs and symptoms | Overall (N = 233) |
|---|---|
| Fever over 38°c | 137 (69.6%) |
| Dry Cough | 124 (62.6%) |
| Muscle Pain | 63 (31.8%) |
| Headache | 21 (10.6%) |
| Chest Pain | 30 (21.8%) |
| Chill | 24 (12.1%) |
| Nausea and Vomiting | 29 (14.6%) |
| Dyspnea | 123 (62.1%) |
| **Saturation $O_2$** | |
| $SPO_2$ <%93 | 128 (54.9%) |
| $SPO_2$ >%93 | 105 (45.1%) |

Table 3
Baseline characteristics of patients infected with COVID-19

| Any Comorbidity Hospitalization (N = 205) | | Death (N = 28) |
|---|---|---|
| Gender | Male 129 (62.9%) | 20 (71.4%) |
| | Female 76 (37.1%) | 8 (28.6%) |
| Diabetes | 32 (15.6%) | 6 (21.4%) |
| Hypertension | 30 (14.6%) | 7 (25.1%) |
| Cardiovascular Disease | 22 (10.7%) | 3 (10.7%) |
| Pulmonary Disease | 12 (5.9%) | 5 (17.9%) |
| Malignancy | 6 (2.9%) | 1 (3.6%) |
| Neural System Diseases | 4 (2.1%) | 1 (3.6%) |
| Renal Disease | 8 (3.9%) | 3 (10.7%) |
| Autoimmunity Disease | 2 (1.1%) | 2 (7.1%) |
| Chronic Liver Disease | 4 (2.1%) | 0 |

On the admission, lymphopenia lower than 1100 µl (58%), neutrophilia more than 6300 µl (25%), and thrombocytopenia (< $125 \times 10^9$L, 12.4%) were detected. Most the patients had increased C-reactive protein level (88.4%), and NLR more than 5 (41%), PLR higher than 200 (45%), SII index of rather than 500 (68.2%), lactate dehydrogenase (72.1%), ESR (59.7%), CPK (29.2%). But in the death group, NLR more than 5 (93%), PLR higher than 200 (71.4%), SII index of rather than 500 (93%) and lymphopenia lower than 1100 µl (79%) had elevated. This data show that the incidence of NLR from 41–93%, PLR from 45–71.4%, and SII index from 68.2–93% were increased in the death groups. Also the incidence of lymphopenia was increased from 58–79%. Finally, NLR, PLR and SII indexes were chosen as the most useful prognostic factor affecting the prognosis for severe patient's incidence by the forward selection procedure (Table 4).

Table 4
Laboratory test of 233 patients with COVID-19

| Blood routine (Normal range) | Stat | Total (N = 233) | Hospitalization (N = 205) | Death (N = 28) |
|---|---|---|---|---|
| Leucocyte (× $10^9$/L, range 3.5–9.5) | Increased | 37 (15.9%) | 20 (9.8%) | 17 (60.7%) |
| | Decreased | 27 (11.6%) | 25 (12.2%) | 2 (7.1%) |
| Neutrophil (× $10^9$/ L, range 1.8–6.3) | Increased | 58 (24.9%) | 36 (17.6%) | 22 (78.6%) |
| | Decreased | 17 (7.3%) | 16 (7.8%) | 1 (3.6%) |
| Lymphocyte (× $10^9$/ L, range 1.1–3.2) | Decreased | 132 (57.6%) | 110 (53.7%) | 22 (78.6%) |
| Platelet (× $10^9$/ L, range 125–450) | Increased | 7 (3.1%) | 6 (2.9%) | 1 (3.6%) |
| | Decreased | 29 (12.4%) | 23 (11.2%) | 6 (21.4%) |
| D-Dimer (mg/L; range < 0.55) | Increased | 19 (8.2%) | 12 (5.9%) | 7 (25.1%) |
| ALT (IU/L, range 0–64) | Increased | 22 (9.4%) | 19 (9.3%) | 3 (10.7%) |
| AST (IU/L, range 8–40) | Increased | 74 (31.8%) | 57 (27.8%) | 17 (60.7%) |
| ALK.P (IU/L, range 25–320) | Increased | 36 (15.5%) | 30 (14.6%) | 6 (21.4%) |
| Total Bilirubin (mg/dL, range 0.4–1.3) | Increased | 24 (10.3%) | 19 (9.3%) | 5 (17.9%) |
| | Decreased | 8 (3.4%) | 8 (3.9%) | 0 |
| Direct Bilirubin (mg/dL, range 0.1–0.3) | Increased | 73 (31.3%) | 62 (30.2%) | 11 (39.3%) |
| | Decreased | 36 (15.5%) | 33 (16.1%) | 3 (10.7%) |
| Bun (mg/dL, range 5–24) | Increased | 59 (25.3%) | 38 (18.5%) | 21 (75.1%) |
| Creatinine (mg/dl, range 0.5–1.4) | Increased | 58 (24.9%) | 40 (19.5%) | 18 (64.3%) |
| CPK (IU/L, range 12–160) | Increased | 68 (29.2%) | 57 (27.8%) | 11 (39.3%) |
| LDH (IU/L, range140–280) | Increased | 168 (72.1%) | 151 (73.7%) | 17 (60.7%) |
| C-Reactive Protein (mg/L, 0.0–6.0) | Increased | 206 (88.4%) | 179 (87.3%) | 27 (96.4%) |
| ESR (mm/h, 2–22) | Increased | 139 (59.7%) | 124 (60.5%) | 15 (53.6%) |
| NA (mEq/L, 135–145) | Increased | 7 (2.9%) | 3 (1.5%) | 4 (14.3%) |

| Blood routine (Normal range) | Stat | Total (N = 233) | Hospitalization (N = 205) | Death (N = 28) |
|---|---|---|---|---|
| | Decreased | 96 (41.2%) | 85 (41.5%) | 11 (39.3%) |
| K (mEq/L, 3.5–5.5) | Increased | 3 (1.3%) | 0 | 3 (10.7%) |
| | Decreased | 49 (21.1%) | 43 (21.1%) | 6 (21.4%) |
| NLR (index, > 5) | Increased | 95 (40.8%) | 69 (33.7%) | 26 (92.9%) |
| | Decreased | 138 (59.2%) | 136 (66.3%) | 2 (7.1%) |
| PLR (index, > 200) | Increased | 104 (44.6%) | 84 (40.9%) | 20 (71.4%) |
| | Decreased | 129 (55.4%) | 121 (59.1%) | 8 (28.6%) |
| SII (index, > 500) | Increased | 159 (68.2%) | 133 (64.9%) | 26 (92.9%) |
| | Decreased | 74 (31.8%) | 72 (35.1%) | 2 (7.1%) |

**Table 5: Comparison of inclusion indicators in the hospitalization and death groups COVID-19.** The values were presented as mean ± SEM.

| Blood routine | Stat | Total (N = 233) | Mean | ±Std. Error Mean | Sig. (2-tailed) |
|---|---|---|---|---|---|
| Leucocyte Count ($10^9$/L) | Death | 28 | 12.3 | 1.17 | |
| | Hospitalization | 201 | 6.1 | 0.23 | **0.0001**** |
| Platelet Count ($10^9$/L) | Death | 28 | 202.1 | 18.1 | 0.480 |
| | Hospitalization | 201 | 215.9 | 6.56 | |
| Neutrophil Count ($10^9$/L) | Death | 28 | 11.08 | 1.12 | **0.0001**** |
| | Hospitalization | 205 | 4.69 | 0.27 | |
| Lymphocyte Count ($10^9$/L) | Death | 28 | 0.79 | 0.07 | **0.0001**** |
| | Hospitalization | 205 | 1.14 | 0.04 | |
| Neutrophil / Lymphocyte Ratio | Death | 28 | 19.28 | 2.93 | **0.0001**** |
| | Hospitalization | 205 | 4.96 | 0.34 | |
| Platelet / Lymphocyte Ratio | Death | 28 | 343.8 | 66.4 | **0.001*** |
| | Hospitalization | 205 | 221.7 | 10.7 | |
| Systematic Inflammatory Index | Death | 28 | 3532.9 | 565.3 | **0.0001**** |
| | Hospitalization | 205 | 1163.5 | 102.9 | |
| BUN (mg/dl) | Death | 26 | 51.2 | 7.18 | **0.0001**** |

| Blood routine (Normal range) | Stat | | Total (N = 233) | Hospitalization (N = 205) | Death (N = 28) |
|---|---|---|---|---|---|
| | Hospitalization | 199 | 18.3 | 0.65 | |
| Creatinine (mg/dl) | Death | 26 | 2.22 | 0.28 | **0.0001**** |
| | Hospitalization | 197 | 1.16 | 0.02 | |
| C-Reactive Protein (mg/l) | Death | 28 | 15.0 | 0.79 | 0.151 |
| | Hospitalization | 205 | 13.2 | 0.44 | |
| SGOT (U/L) | Death | 23 | 80.1 | 20.2 | **0.0001**** |
| | Hospitalization | 179 | 40.6 | 2.43 | |
| SGPT (U/L) | Death | 23 | 48.8 | 12.1 | 0.176 |
| | Hospitalization | 179 | 37.4 | 2.61 | |
| Alkaline Phosphatase (U/L) | Death | 21 | 271.5 | 17.4 | 0.339 |
| Total Bilirubin (mg/dl) | Hospitalization | 174 | 253.1 | 7.76 | **0.004*** |
| | Death | 19 | 1.44 | 0.31 | |
| | Hospitalization | 161 | 0.91 | 0.05 | |
| Direct Bilirubin (mg/dl) | Death | 19 | 0.59 | 0.21 | **0.007*** |
| | Hospitalization | 161 | 0.31 | 0.03 | |
| Creatine Kinase (IU/L) | Death | 20 | 438.8 | 169.3 | 0.315 |
| | Hospitalization | 163 | 258.1 | 48.1 | |
| Lactate Dehydrogenase (IU/L) | Death | 18 | 820.5 | 122.1 | **0.001*** |
| | Hospitalization | 155 | 534.4 | 26.5 | |
| Sodium (mEq/L) | Death | 25 | 136.40 | 1.43 | 0.698 |
| | Hospitalization | 184 | 136.04 | 0.28 | |
| Potassium (mEq/L) | Death | 25 | 4.2 | 0.17 | **0.001*** |
| | Hospitalization | 183 | 3.9 | 0.03 | |
| ESR (mm/h) | Death | 15 | 56.1 | 4.81 | **0.048*** |
| | Hospitalization | 147 | 46.3 | 2.17 | |
| D-Dimer (mg/L) | Death | 7 | 1.24 | 0.06 | **0.001*** |
| | Hospitalization | 27 | 0.64 | 0.08 | |

Independed sample t test show that the inflammatory indicator levels were significantly elevated in the patients with mild/moderate or severe COVID-19 when compared with the death groups (Table 5). In addition, serum BUN and creatinine levels in group death have been significantly increased ($P < 0.0001$).

# Radiography findings

In Table 6, radiological data is summarized on admission. The typical chest CT pattern findings in patients with confirmed diagnosis of RT-PCR COVID-19, include GGOs pattern (30.3%), patchy consolidations (11.4%, Fig. 1A) and GGO with consolidations (mixed, 51.2% [see Fig. 1B]). Pure GGO lesions (Fig. 1C, I, II) can be the early appearance of SARS-CoV-2 pneumonia. Interestingly, 15 (7.1%) of participants had clear chest CT scan findings on admission in hospital. Also exception of NLR and SII indicator in comparison between GGO and mixed pattern ($P < 0.01$), there was no significant difference between two groups in laboratory test and imaging manifestations (Supplementary Fig. 1). However this result indicate that alone chest CT findings are nonspecific for COVID-19 pneumonia detection and have been suggested as main evidence of clinical diagnosis when RT-PCR results can be affected by specimen errors and low virus load.

Table 6
Radiological data of patients with COVID-19

| | | | Lesion Location | | | | Total |
|---|---|---|---|---|---|---|---|
| | | | No Lesion | Right lateral | Bilateral | Left lateral | |
| **Density Pattern** | Clear | Count (% ) | 15 (7.1%) | 0 | 0 | 0 | **15 (7.1%)** |
| | GGO | Count (% ) | 0 | 22 (10.5%) | 24 (11.5%) | 17 (8.3%) | **63 (30.3%)** |
| | Consolidation | Count (% ) | 0 | 5 (2.5%) | 13 (6.4%) | 5 (2.5%) | **23 (11.4%)** |
| | Mixed | Count (% ) | 0 | 5 (2.5%) | 95 (46.9%) | 3 (1.8%) | **103 (51.2%)** |
| Total | | Count (% ) | 15 (7.1%) | 32 (15.5%) | 132 (64.8%) | 25 (12.6%) | **204 (100%)** |

# Discussion

Current study is a descriptive report on the epidemiology and clinical/paraclinical characteristics of 233 patients with laboratory proven evidence of COVID-19 attending Buali Hospital, Zahedan, Iran. It represents the recent status of the COVID-19 in east of Iran where biggest state of Iran is located. Collectively, 1,911

patients who were suspected to carry the disease were referred to our center over a three month period, of which approximately 629 patients had mild/moderate to serious, sometimes fatal, pneumonia and were hospitalized. Given RT-PCR is regarded as reference standard method for diagnosis of SARS-CoV-2 infection [11], the paraclinical data of only 37% (233/629) of patients with positive RT-PCR results were investigated in the present study.

Human coronavirus is one of the main viral pathogens involving respiratory system. SARS-CoV and MERS-CoV besides four other human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1) are the main pathogenic viruses related to coronavirus family causing severe respiratory syndrome and mild upper respiratory disease [12]. The major SARS-CoV outbreak affected 8,422 patients of 29 countries during 2002–2003 [13, 14]. Also, in 2012, MERS-CoV was emerged in Middle East countries [15]. Although, the genomic sequence of SARS-CoV-2 has been shown to be relatively different from the six other coronavirus subtypes but it can be classified as beta coronavirus [12]. In case of SARS-CoV and MERS-CoV, the viruses can be transmitted directly from civets and dromedary camels to humans, respectively, and bats were considered as the origin of both viruses, but the origin of SARS-CoV-2 is still not clear and needs further investigation [12, 16]. Rate of transmission is not exactly documented for SARS-CoV-2; however, human to human transmission has been evidenced [7, 12]. In concert with previous reports, it has been revealed that the clinical manifestations of COVID-19 mimic those presented in SARS-CoV [4, 7, 12, 17]. Fever and cough were the most predominant symptoms manifested in 80% and 70% of our patients respectively. However, gastrointestinal upsets were infrequently presented (10%), which suggests a different viral tropism and pathogenesis in comparison with SARS-CoV, MERS-CoV, and seasonal influenza [7, 18–20]. The frequency of afebrile patients suffering from COVID-19 (20%) is more frequent than in SARS-CoV (1%) and MERS-CoV infection (2%) [7, 15] implying that presence of fever is not a trustworthy finding to be focused in case definition because afebrile patients will be missed. Similar to previous reports [4, 7, 12], reduced absolute lymphocytes count, and elevated level of CRP and ESR were the main laboratory findings. Damage to T lymphocytes might be a contributing factor leading to substantial decrease in total lymphocytes count and exacerbation of patient's status [21] as we observed statistically significant abnormalities in laboratory findings (including lymphopenia, elevated NLR, PLR and SII) of patients who expired when compared with non-severe disease. In consistent with our result, a previous study conducted by Liu, et al [3], documented NLR as the independent risk factor for prediction of severe illness in patients with SARS-CoV-2 infection which should rapidly hospitalized in ICU. So that, in 50% of patients with age $\geq$ 50 who had NLR $\geq$ 3.13 severe form of the disease were observed [3, 10]. Furthermore, in another study, a correlation between elevated PLR and the length of hospitalization day was evidenced and it has been concluded that if PLR increased more during treatment, the patient needs longer hospitalization day and had greater possibility of severe pneumonia [22]. It is concluded that lymphocytes, especially T lymphocytes, are the main cell to be targeted and consumed by SARS-CoV-2, as does SARS-CoV [21]. Virus particles pass across the respiratory mucosa and attack other cells, stimulate a cytokine storm in the body, and generate a cascade of immune responses, leading to changes in peripheral white blood cells and immune cells such as lymphocytes [12]. Patients who suffered from severe form of COVID-19 (18%) required ICU hospitalization and oxygen therapy. Consequently, ARDS and septic shock progressed rapidly in some of our patients, which were eventually followed by multiple organ failure and death. As a result, level of creatinine, BUN and total/direct bilirubin were significantly increased in deceased patients when compared to alive patients which suggesting acute kidney and liver

injury in our deceased patients similar to whatever evidenced in former report [23]. Therefore, early diagnosis and promptly treatment initiation of critically ill individuals is issue of crucial importance [12]. Only one patient in our investigation was medical worker. The mortality rate of SARS-CoV and MERS-CoV has been reported as more than 10% and 35%, respectively [24, 25]. The rate of mortality in our SARS-CoV-2 infected population was 12%, resembling to previous study [12]. Nonetheless, the rate of deaths might increase because many patients are still hospitalized. It necessary to be noted that since patients who had uncomplicated illness and who did not need medical attention were not included in our study, the rate of case fatality in a real world scenario might be even lower. COVID-19 was more commonly observed in men than women (63% vs 37%) in our study. This gender preponderance was in agreement with previous studies [4, 7, 12]. Also, higher rate of MERS-CoV and SARS-CoV infection were documented in males than females [26, 27]. The lower frequency rate of COVID-19, MERS-CoV and SARS-CoV infection in females are thought to be attributed to the protection originating from sex hormones and X chromosome, which play contributing role in innate and adaptive immunity [28]. Additionally, it has been documented that COVID-19 is more probably to occur in older adult males due to weaker immune functions particularly those with chronic underlying diseases [12]. Our patient's age ranged from 16 to 90 years with a mean age of 49 years. The data was in consistent with the previous studies which more and less reported similar mean age [7, 12]. The highest positive rate of COVID-19 RT-PCR was observed in age group 40–60 years. Since, our aim was to investigate the COVID-19 patients with positive RT-PCR as reference method, of 629 hospitalized patients who were clinically suspected cases of COVID-19 and also had initial positive CT scan suggesting COVID-19, only small quantity of our subjects had positive RT-PCR assay suggesting two scenarios: first, it may be indeed be true to say that the sensitivity rate of RT-PCR is as low as 37% which somehow has been also demonstrated in previous studies and may be justified by a list of confounding factors which is regarded to influence the result of RT-PCR and lead to false-negative including: improperly collected, transported or handled specimens, presence of amplification inhibitors in the specimen or inadequate numbers of organisms [11, 29, 30]. Second, due to the overlap of CT imaging patterns between COVID-19 and other viral pneumonia, false-positive cases of COVID-19 may be identified on chest CT scan [11]. Nevertheless, given the rapidly spreading of COVID-19, the priority should be to identify and isolate any suspicious CT scan case in order to administer appropriate treatment. By the way, in the context of disease control, some false-positive cases may be acceptable [11]. Therefore, one negative result of RT-PCR does not rule out SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions and treatment.

# Conclusions

As a result, serially performance of RT-PCR test along with CT scans is highly recommended. In patients with negative RT-PCR tests, a combination of a history of direct contact with proven cases, clinical manifestations and typical CT imaging features should be collectively used to detect patients with COVID-19. Elevated NLR, PLR and SII can be considered as prognostic and risk stratifying factor of severe form of disease.

# Abbreviations

**COVID-19**
Coronavirus disease 2019

**SARS-CoV-2**
Severe acute respiratory syndrome coronavirus 2
**WHO**
World health organization
**ICU**
Intensive care unit
**ARDS**
Acute respiratory distress syndrome
**CT**
Computed tomography
**GGOs**
Ground-glass opacities
**IL**
Interleukin
**CRS**
Cytokines release syndrome
**VTM medium**
Virus transport medium
**CRP**
C-reactive protein
**ESR**
Erythrocyte sedimentation rate
**LFT**
Liver function test
**CPK**
Creatine phosphokinase
**LDH**
Lactate dehydrogenase
**FAM**
Fluorescein amidites
**VIC**
Victoria
**RT-PCR**
Real time reverse transcriptase polymerase chain reaction
**NLR**
Neutrophil to lymphocyte ratio
**SII**
Systematic immune-inflammation index
**PLR**
Platelet to lymphocyte ratio

# Declarations

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### Availability of data and materials

The datasets used or analyzed during the current study, as well as the study protocol, are available from the corresponding author on reasonable request.

**Competing Interests:** No conflict of interest

**Ethics approval and consent to participate:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1399.) and written consent was obtained from the patients or their guardians.

### Consent for publication

Not applicable.

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### Author's contributions

MR analyzed and interpreted the data, drafted the manuscript and revised the manuscript. SM reviewed the medical records. KA drafted the manuscript. SA and FH analyzed the data. All authors have read and approved the final manuscript for publication.

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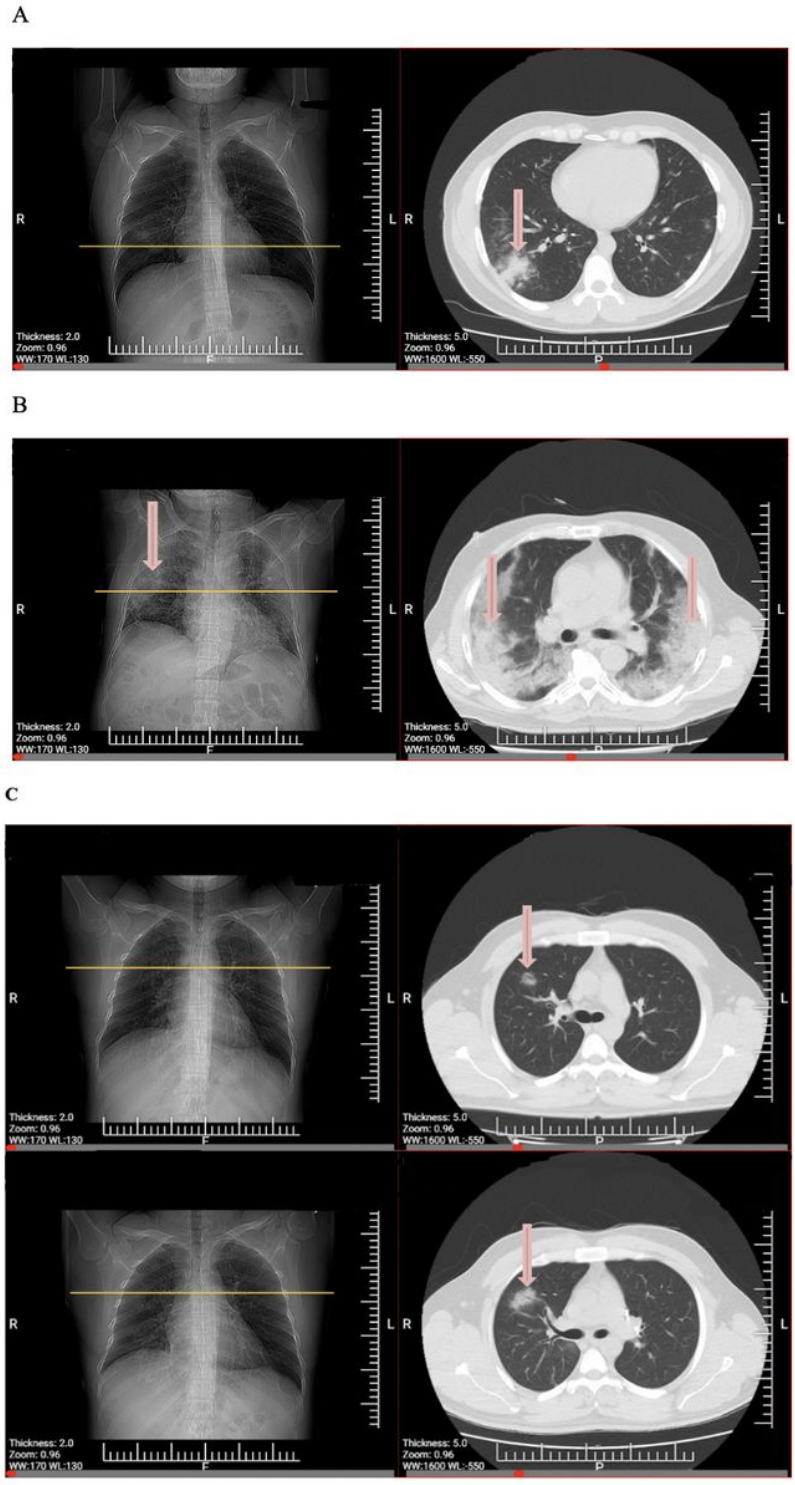
# Figures




## Figure 1

A: CT findings of confirmed COVID-19 pneumonia. Consolidation pattern, a young patient presented with fever (38.6°C) and exposure history. Chest CT acquired on March 28, 2020 showed consolidation lesions (arrows) in the lobe of right lung. B: CT findings of severe type confirmed COVID-19 pneumonia. A old patient presented with fever and respiratory occurs and requires mechanical ventilation in ICU. Chest CT was got on the same day as positive RT-PCR with distributed ground-glass opacities with consolidation (arrows) in the lobes of right and left lung. C: CT findings of confirmed COVID-19 pneumonia. Ground-glass opacity (GGO)

pattern, A young patient presenting without fever with lab-confirmed COVID-19. I: Chest CT acquired 2 days before the first positive RT-PCR test showed a rounded GGO in the right lung upper lobe (arrow). II: Follow-up chest CT-Scan after 3 days showed the size enhancement of the lesion (arrow).

## Supplementary Files

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- SupplementaryFigure.docx