



## Original Article

## Clinical Presentations of Iranian Confirmed COVID-19 Patients at the Admission Time: A Preliminary Retrospective Study

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### ABSTRACT

#### Article history

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#### Keywords

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**Background and Aims:** The current preliminary study aimed to assess the clinical symptoms of the 67 Iranian COVID-19 patients and investigate the possible beneficial effects of the naproxen compared to the standard therapeutic regimen.

**Materials and Methods:** We assessed 67 COVID-19 patients. All COVID-19 cases were confirmed by computed tomography (CT) and real time-polymerase chain reaction tests. We evaluated the clinical symptoms of the patients at the admission time. Also, a group of 28 patients received naproxen besides their standard treatment. Clinical presentations, radiographic features, white blood cells (WBC) in peripheral blood, hemoglobin, platelets, C-reactive protein, erythrocyte sedimentation rate, blood urea nitrogen, lactate dehydrogenase, Albumin, and Creatine Phosphokinase were evaluated.

**Results:** The patients' clinical symptoms show that cough (89.6%) was the most repeated sign at the admission time, followed by fever at 78.7%, fatigue at 70%, and myalgia at least 64.2%. Unilateral slight ground-glass opacity was the most abundant presentation by 64.1% in CT. The laboratory assessment in patients indicates that mean WBC was  $6193 \pm 3258$  ( $\times 10^6/L$ ), and mean lymphocyte was  $27.8 \pm 12\%$ . The survival rate and the hospitalization days for patients with or without the Naproxen regimen were not statistically significant.

**Conclusion:** The most common clinical symptoms in Iranian patients with COVID-19 at the admission time include cough, fever, fatigue, and myalgia. Based on the current study results, the survival rate and the hospitalization days for patients with or without Naproxen usage were not statistically significant. The laboratory parameters could not show any particular statistically significant differences.

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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible infection, first identified in December 2019, Wuhan city, Hubei Province, in China [1, 2]. The causative agent of this serious illness is termed "Coronavirus Disease 2019 (COVID-19)" by the World Health Organization, temporarily known as 2019 novel (2019-nCoV), and then formalized into "SARS-CoV-2" by the International Committee on Taxonomy of Viruses (ICTV) [3-5]. Coronaviruses (CoVs) belong to the subfamily of *Orthocoronavirinae* in the family of *Coronaviridae*; these viruses categorized in Nidovirales order. The genome of the coronaviruses is large, with a size range of 27 to 34-kilo bases. These viruses are enveloped positive-sense single-stranded ribonucleic acid [6] and can be classified into four genera: alpha coronaviruses, beta coronaviruses, gamma coronaviruses, and delta coronaviruses [7-9]. Betacoronavirus and alpha coronaviruses can infect humans. Betacoronavirus such as MERS-CoV, SARS-CoV, and SARS-CoV-2 are often held responsible for respiratory diseases and epidemic or pandemic conditions with variable clinical manifestations ranging from asymptomatic disease to lethal lung inflammation. There have been documented outbreaks caused by these strains in recent years [10, 11]. After an average 4 to 14 days incubation period, in symptomatic conditions, the primary manifestation of COVID-19 are fever, dry cough, fatigue, sputum production, myalgia, dyspnea, chest tightness, and body aches which can be accompanied by headaches and gastrointestinal

presentations and can last for several days. Patients have fewer complaints from nasal congestion, runny nose, sore throat, vomiting, and diarrhea. During the first week after symptoms onset, patients may experience dyspnea and/or hypoxemia, which is quickly followed by septic shock, acute respiratory distress syndrome, metabolic acidosis disorders, coagulation abnormalities, and organ dysfunction [6, 11, 12]. Older patients with background diseases need more supportive treatments, such as mechanical ventilation, intensive care unit (ICU) admission, as they have higher fatality rates [11, 12].

Considering the quick distribution of COVID-19, lack of vaccines, and therapeutic drugs, finding effective strategies to resolve this global crisis seems essential [13]. The therapeutic options for COVID-19 are progressively reviewed [14, 15]. Currently, based on the clinical trials, it seems that only Remdesivir and Dexamethasone are beneficial. However, there are many ongoing clinical trials to assess the other therapeutic options for COVID-19 [14].

The current preliminary study aimed to assess the clinical symptoms of the 67 Iranian COVID-19 patients and investigate the possible beneficial effects of the Naproxen administration compared with the standard therapeutic regimen.

## Materials and Methods

### Patient's selection and COVID-19 diagnosis

Patients were included based on the following inclusion criteria, confirmed polymerase chain reaction (PCR) result for SARS-CoV-2, written consent for including in this research, and age

more than 18 years. The patients were referred to the Iran University of Medical Science hospitals from May to April of 2020. The COVID-19 diagnosis was confirmed based on the national guideline criteria [16]. The diagnosis was performed based on the clinical manifestation, computing tomography (CT) findings, and reverse transcriptase real-time polymerase chain reaction (PCR) test for SARS-CoV-2.

#### **Clinical data and therapeutic regimen**

The clinical data for the current study, including the clinical manifestations and demographical data, were gathered at the time of the first admission by checklist. The standard protocols of the COVID-19 treatment from May to April were used for patients based on the national guidelines at the admission time after the confirmation of the COVID-19 by CT and the real-time PCR test [16]. The treatment included hydroxychloroquine and Lopinavir-Ritonavir, and a group of patients was treated by additional Naproxen 250 mg twice a day.

#### **Laboratory parameters**

The laboratory and radiologic features from patients were collected during administration and visits after the written ethical confirmation. Clinical presentations, radiographic features, and laboratory features were evaluated. The white blood cells (WBC) in peripheral blood, hemoglobin, and platelets were assessed by Sysmex XE-2100 (Sysmex, Kobe, Japan). Meanwhile, C-reactive protein (CRP) (ENiSon, Tehran, Iran), erythrocyte sedimentation rate (ESR) (by Westergren method) and blood urea nitrogen (BUN), lactate dehydrogenase (LDH), Albumin (Alb), and creatine phosphokinase

(CPK) were evaluated by commercially available kits (Parsazmon, Iran). The ethical committee of the Iran University of Medical Science approved all the procedures of the current study (Ethical code: IR.IUMS.REC.1399.001).

#### **Statistical analysis**

The statistical analysis was performed by SPSS version 22 (SPSS Inc., Chicago, Illinois, USA). The chi-squared test was used to assess the nominal variables, and the Mann-Whitney U test was used for nominal and numerical variables evaluation. Also, the significance level was considered as P-value less than 0.05.

## **Results**

#### **Demographical features**

In the current study, we evaluated 67 Iranian patients with COVID-19. The demographical assessment indicates 33 (49.3%) males and 34 (50.7%) females. Also, the mean age  $\pm$  SD of the referred patients was  $53.5 \pm 18.9$  years. Furthermore, there were 28 patients in the Naproxen group and 39 patients in the standard treatment group. There were 16 male (57%) and 12 (43%) female in Naproxen group ( $p > 0.05$ ). Besides, 11 (16.4%) were reported close contact with COVID-19 patients in the last few days ( $p > 0.05$ ). Smoking evaluation of the patients shows that 2.9% of the patients are active smokers, and there was no statistical difference between the symptoms or the outcome in smokers ( $p > 0.05$ ). Patients with background disorders are considered risk group patients, including 42% of patients in the current study. Risk group patients were statistically significant with age (more than 65 years old) ( $p = 0.04$ ). The background conditions of the patients reveal that cardiovascular disorders are the most

abundant condition in high-risk group patients by 32% and followed by hypertension (28%). Other background disorders included diabetes (16%), chronic respiratory disorders (16%), and bronchiectasis (8%), and patients exposed to chemical weapons during the war.

### Clinical presentations

The patients' clinical symptoms show that cough (89.6%) was the most repeated sign at the admission time. Also, other clinical presentations included fever (78.7%), fatigue (70%), myalgia (64.2%), headache (47.8%), chills (46.3%), dyspnea (46%), nausea (38%), sputum production (34%), diarrhea (32%), sore throat (25.4%), and dizziness (20%). The mean  $\pm$  SD fever temperature was  $37.9 \pm 0.63$  °C. Also, the mean respiratory rate  $\pm$  SD was  $18.7 \pm 3.5$ , and the mean  $\pm$  SD oxygen saturation (SO<sub>2</sub>) was  $95.07 \pm 3.4\%$ . There was no statistically significant difference between any clinical symptom with age, gender, or para clinical conditions ( $p > 0.05$ ).

### Paraclinical assessment

The chest CT assessment of the included patients indicated that diffused bilateral ground-glass opacity (GGO) was seen in 18.8% of the patients. Bilateral GGO and fibrotic signs were seen in 3.1%, and bilateral GGO and dens opacity was observed in 1.6%. Unilateral slight GGO opacities were the most abundant presentation by 64.1%. Patchy GGOs and slight opacities frequencies were 3.1% and 9.4%, respectively. The chest CT and other clinical or laboratory findings did not show any statistically significant associations ( $p > 0.05$ ). The laboratory assessment at the admission time in patients indicates that mean  $\pm$  SD of WBCs were

$6193 \pm 3258$  ( $\times 10^6/L$ ), mean  $\pm$  SD lymphocyte (%), and neutrophils% in the differential count of WBCs in peripheral blood was  $27.8 \pm 12\%$  and  $64.3 \pm 12.3$ , respectively. Other assessed hematological parameters included hemoglobin and platelets mean  $\pm$  SD, which were  $12.3 \pm 1.3$  g/dL and  $222 \pm 88$  ( $\times 10^6/L$ ), respectively. Inflammatory markers show that the mean  $\pm$  SD of CRP was  $44.7 \pm 40.8$  mg/dL, and ESR was  $41 \pm 26.7$  mm/hr. Biochemical analysis was limited to the BUN, LDH, Alb, and CPK. The mean  $\pm$  SD value for the mentioned biochemical parameters includes BUN, LDH and Alb were  $17 \pm 14$  mg/dL,  $380 \pm 186$  U/L,  $4 \pm 0.4$  g/dL, respectively, and  $116 \pm 100$  U/L for CPK. The statistical assessment shows a significant difference between Hemoglobin and Creatinine with gender ( $p < 0.05$ ). Also, the ESR was statistically significant, mostly in people over 65 years ( $p = 0.014$ ) (Table 1).

### Therapeutic regimens and hospitalization days

Hospitalization assessment shows that 44 (65.7%) of patients did not need any hospitalizations and were approached as an outpatient with quarantine consideration. Meanwhile, 12 (17.9%) of patients were hospitalized in general sections with quarantine consideration, and 7 (10.4%) of the patients needed ICU admission. After 20 days of follow-up of the patients, all were recovered and discharged, and three patients were expired. The mean age  $\pm$  SD of expired patients was  $75 \pm 3$  years, and all had background disorders (all three had hypertension). Also, expire rate was statistically significantly associated with WBC ( $p = 0.02$ ).

**Table 1.** The laboratory finding is COVID-19 patients by considering the age and gender

Marker	Gender			Age (years)			Outcome		
	Male	Female	p-value	< 65	> 65	p-value	Recovered	Expire	p-value
<b>WBC</b> (x10 <sup>6</sup> /L)	6568 ± 3431	5867 ± 3119	> 0.05	6483 ± 3283	6739 ± 4414	> 0.05	5879 ± 2804	11966 ± 4708	<b>0.02*</b>
<b>Lymphocyte</b> (%)	28 ± 12	27.9 ± 11.9	> 0.05	27 ± 10	25 ± 13	> 0.05	16 ± 11	23 ± 11	> 0.05
<b>Neutrophils</b> (%)	63.4 ± 12.3	65.2 ± 12.5	> 0.05	63 ± 10	67 ± 13	> 0.05	63 ± 12	76 ± 11	> 0.05
<b>Hb (g/dL)</b>	13.4 ± 1.4	1.2 ± 1.1	<b>0.002*</b>	13 ± 1.3	12 ± 1.4	> 0.05	12 ± 1.4	12 ± 1.5	> 0.05
<b>Platelets</b> (x10 <sup>6</sup> /L)	200 ± 75	239 ± 95	> 0.05	216 ± 97	216 ± 103	> 0.05	225 ± 90	186 ± 39	> 0.05
<b>CRP</b> (mg/dL)	37 ± 24	50 ± 49	> 0.05	38 ± 25	70 ± 64	> 0.05	44 ± 41	63 ± 12	> 0.05
<b>ESR</b> (mm/hr)	32 ± 19	47 ± 29	> 0.05	32 ± 16	62 ± 34	<b>0.014*</b>	42 ± 26	34 ± 30	> 0.05
<b>BUN</b> (mg/dL)	16 ± 8	17 ± 9	> 0.05	17.8 ± 15	17 ± 13	> 0.05	16 ± 13	27 ± 23	> 0.05
<b>Cr (mg/dL)</b>	1.2 ± 0.3	1.07 ± 0.4	<b>0.02*</b>	1.02 ± 0.18	1.2 ± 0.48	> 0.05	1 ± 0.2	1.6 ± 0.8	> 0.05
<b>LDH (U/L)</b>	337 ± 14	407 ± 174	> 0.05	373 ± 171	406 ± 187	> 0.05	382 ± 155	341 ± 224	> 0.05
<b>CPK</b>	121 ± 117	114 ± 94	> 0.05	99 ± 96	114 ± 97	> 0.05	116 ± 99	120 ± 138	> 0.05

\*Statistically significant difference; WBC= White blood Cell; Hb= Hemoglobine; CRP= C-reactive protein; ESR= Erythrocyte sedimentation rate; BUN= Blood urea nitrogen; Cr= Creatinine; LDH= Lactate dehydrogenase; CPK= Creatine phosphokinase

All 67 patients received standard therapeutic regimens, as mentioned before. In addition, 28 patients received the naproxen as complementary for the therapeutic regiment. The survival rate and the hospitalization days for patients with or without the naproxen were not statistically significant ( $p > 0.05$ ). Also, the laboratory or CT parameters did not show any statistically significant difference between patients who received naproxen or standard treatment patients ( $p > 0.05$ ).

## Discussion

SARS-CoV-2 is a highly transmissible pathogen, and the virus spreads quickly around the world. The virus led to 199 million confirmed cases, and 4 million deaths all

around the world and 3.9 million confirmed cases, and 91407 deaths in Iran by the date of 3 Aug 2021 [2]. There are different studies and reports from Iranian COVID-19 patients [17-19]. The current preliminary study aimed to assess the clinical symptoms of the 67 Iranian COVID-19 Patients and investigate the possible beneficial effects of the naproxen compared to the standard therapeutic regimen. In the current study, the demographical assessment indicates that 33 (49.3%) males and 34 (50.7%) females. In addition, the mean age ± SD of the referred patients was 53.5 ± 18.9. Furthermore, 11 (16.4%) were reported close contact with COVID-19 patients in the last few days. The patients' clinical symptoms show that the Cough (89.6%) was the most repeated signed at

the admission time and followed by fever 78.7%, fatigue 70%, and myalgia 64.2%. Unilateral slight GGO opacities were the most abundant presentation by 64.1%. The laboratory assessment in patients indicates that mean WBC was  $6193 \pm 3258$  ( $10^6/L$ ), and mean  $\pm$  SD lymphocyte% was  $27.8 \pm 12\%$ . The survival rate and the hospitalization days for patients with or without the naproxen were not statistically significant.

In the conducted study by Pan et al. [18], the assessment of the 63 COVID-19 patients indicated that patchy ground glass (85.7%) and GGO (22.2%) are the most dominant radiologic finding in COVID-19 patients. Unlike Pan's study in our current study, unilateral slight GGO opacities were the most abundant presentation (64.1%), followed by diffused bilateral GGO (18.8%). Meanwhile, in the study conducted by Guan and colleagues [19], 1099 COVID-19 patients from China were assessed, and the GGO (56.4%) and local patchy (41%) were the most abundant radiologic results. These differences between our current report and conducted studies in this field are reasonable, and they can be justified by considering the study population, different demographical parameters, and a wide range of radiological presentations in COVID-19 patients. Also, Guan and colleagues [19] reported fever as the most abundant symptom of the disease and followed by cough (68%), and other symptoms including fatigue (38%), myalgia (11%), diarrhea (3.8%), nausea or vomiting (5%), sore throat (14%), and headache (13.5%). This pattern of the clinical presentation by the domination of the fever and

less frequent cough was reported by other studies [20-23].

In contrast, our current report reflected a cough (89.6%) as the most frequent clinical symptom at admission, followed by fever (78.7%). Bajema et al. investigated the clinical presentations of 210 COVID-19 patients from the USA. The results indicated that cough (90%) was the most common and followed by fever (68%) in these patients [22]. Considering all these results, it could be concluded that the most frequent symptoms are fever and cough, followed by other symptoms and differences between these studies. Our current retrospective study could be justified by considering the study population and demographical differences.

The laboratory assessment at the admission time in patients indicates that mean  $\pm$  SD of WBCs were  $6193 \pm 3258$  ( $\times 10^6/L$ ), mean  $\pm$  SD lymphocyte%, and neutrophils% in the differential count of WBCs in peripheral blood was  $27.8 \pm 12\%$  and  $64.3 \pm 12.3$ , respectively. Inflammatory markers show that the mean  $\pm$  SD of CRP was  $44.7 \pm 40.8$  mg/dL, and ESR was  $41 \pm 26.7$  mm/hr. Conducted studies reported the inflammatory markers up-regulation such as ESR and CRP, WBC elevation, and lymphocyte decrease in COVID-19 patients at the admission time as diagnostic features, repetitively [24]. This result is in confirmation by our current study. The biochemical analysis represents LDH elevation in COVID-19 patients, and various studies report the LDH up-regulation. In this regard, the LDH level was introduced as a risk factor for disease severity [25, 26].

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as a treatment for inflammation and pain worldwide. These drugs' anti-inflammatory effects lay on the down-regulated prostaglandin production during the cyclooxygenase cycle of the arachidonic acid. Naproxen is a well-known and widely-used NSAID [17, 27]. Different studies suggested antiviral activity for these drugs besides their anti-inflammatory role [28, 29]. The benefits of NSAIDs in viral respiratory disease were comprehensively reviewed by Yousefifard et al. [30]. In the conducted study by Vahedi and colleagues [31], the use of prednisolone was more beneficial for reducing hospitalization duration in COVID-19 patients than in naproxen (in combination with azithromycin and lopinavir/ritonavir). The result of the current study in using naproxen for COVID-19 patients confirms the mentioned studies above. There were no statistically significant differences between patients who received naproxen and those who just gave a standard

treatment. Also, it should be considered that one of the retrospective study limitations was the limited number of patients and follow-up days. Considering this limitation and the current study setting, we could not suggest a definite conclusion regarding naproxen administration in COVID-19 patients.

## Conclusion

The most common clinical symptoms in Iranian patients with COVID-19 at the admission time were cough, fever, fatigue, and myalgia. Based on the current study results, the survival rate and the hospitalization days for patients with or without the naproxen were not statistically significant. Further studies and clinical trials are required for a definite conclusion about the naproxen administration.

## Conflict of interest

There is no conflict of interest between authors in this study.

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