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COVID-19 severity and risk factors in Iranian patients with rheumatic diseases

Farnaz Akbari Kamrani[1], Nahid Kianmehr[2*], Vahan Moradians[3], Ali Sepyani[4], Anousheh Haghighi[2]

[1] Resident of Internal Medicine, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [2] Professor of Rheumatology , Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [3] Assistant professor of Pulmonology, Department of Internal Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Iran. [4] Medical student, Tehran branch, The Islamic Azad University, Tehran, Iran.

Since the beginning of COVID-19 pandemic, there was a concern whether patients with rheumatic diseases are at increased risk of severe COVID-19 in terms of the multi-system involvement, underlying comorbidities, and anti-rheumatic medications. We intended to evaluate the severity and mortality of COVID-19 in these patients, as well as the demographic, laboratory, and clinical risk factors associated with the disease. In patients with plasma chane reaction positive COVID-19 admitted to the hospital, laboratory and clinical measures after hospitalization and severity measures such as length of hospitalization, hospitalization in the intensive care unit, and mortality were compared between patients with and matched patients without a history of rheumatic disease. Moreover, risk factors associated with COVID-19 mortality in the case group were calculated by odds ratio (OR). We found no statistically significant difference in COVID-19 severity between the two groups (mortality rate of 22% in case and 25% in control groups, P-value = 0.83). Except for platelet markers, which were considerably greater in the case group despite not being related with the severity of the illness, the available laboratory measurements did not vary between these groups. In addition, we showed that age over 65 years (OR = 4.06), lactic dehydrogenase level, percentage of lung involvement and ischemic heart disease (OR = 6.24) were associated with poorer outcome in the patients with rheumatic diseases. Hence, we found that usage of conventional synthetic disease modifying anti-rheumatic drugs (OR = 2.3, P-value = 0.48) or daily treatment dose of prednisolone >10 mg/d (OR = 1.04) were not associated with COVID-19 mortality. Although the patients with rheumatic disease may be at increased risk of developing a COVID-19 infection, they do not experience more severe disease

Keywords: COVID-19; Rheumatic diseases; Rheumatoid arthritis; Platelet; Prednisolone

Introduction

Because of the high mortality and high contagiousness of acute respiratory disease caused by SARS-CoV-2, which was initialy initially discovered in Wuhan in December 2019, it was designated as the COVID-19 pandemic by the World Health Organization (WHO) in March 2020. As of early March 2022,

*Corresponding Author: Nahid Kianmehr, Department of Rheumatology, RasoolAkram Medical Complex, Niayesh Street, Sattarkhan Avenue, Tehran, Iran. E-mail: kianmehr.n@iums.ac.ir

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the WHO has reported more than 440 million people diagnosed and more than 6 million deaths worldwide from COVID-19 since the start of the pandemic (www.who.int). There were many studies trying to address the possible risk factors for the severity and poor outcome of disease. Age [1], underlying diseases, such as cardio-vascular and chronic pulmonary diseases, renal failure and immunodeficiency [2], were reported as potential risk factors for severe from of the disease and mortality.

After beginning of the pandemic, there was an increasing concern regarding the treatment process and prognosis of patients, with underlying autoimmune and inflammatory diseases. Among these patients, those with rheumatic diseases were at higher risk of mortality and more severe COVID-19 because of the inflammatory nature of their conditions, underlying comorbidities, multisystem involvement, and treatment with immunosuppressive medications [3]. Several studies compared COVID-19 prevalence and clinical outcome in the patients with inflammatory rheumatic diseases with others. For example, in one of the first studies, increased COVID-19 risk in patients with the rheumatoid arthritis was suggested [4]. It was reported that rheumatoid arthritis patients were at increased risk of hospitalization, and mortality in terms of COVID-19 and the effect of underlying diseases, treatments, race, gender and other factors was estimated as risk factors [5].

Furthermore, several studies and wide registry projects in different centers were carried out to record the data and follow the conditions of rheumatic diseases' patients diagnosed with COVID-19 [6, 7]. According to some early findings, longer hospital stays and greater mortality rates were linked to risk variables such older age, underlying disorders, and higher Prednisolone treatment doses [8]. On the other hand, based on clinical observations suggesting the use of some medications effective for rheumatic diseases, such as tocilizumab (anti-interleukin 6) in control of cytokine storm in patients with severe COVID-19 [10] and hydroxychloroquine which was widely used in the beginning of pandemic as first line treatment [11], some studies were carried out in favor or against using these drugs [12, 13]. In addition, a number of clinical studies have been initiated for the administration of several of these drugs in the management of severe COVID-19 [10]. For instance, hydroxychloroquine's effects in vitro and in vivo in the prevention and treatment of COVID-19 have been documented [14]. In another study, it was hypothesized that the patients with systemic lupus erythematosus under treatment with hydroxychloroquine are resistant to COVID-19 [15], which was counteracted by another study in which 19 out of 110 COVID-19 patients with rheumatic diseases were lupus patients under treatment[13]. Thus, other studies, considered the effect of other immunomodulatory drugs, such as anti-IL6, JAK inhibitors and intavenous immunoglobulin in the treatment of COVID-19 [16].

In this study, we compared the clinical outcome of COVID- 19 among the patients with or without underlying rheumatic diseases. Further. we compared the COVID-19 severity risk factors, such as platelet markers [17, 18] between these two groups. Besides, the effect of previous medications for underlying rheumatic diseaseson COVID-19 clinical outcome were assessed.

Materials and Methods

The study population were COVID-19 patients with a positive plasma chane reaction (PCR) test. Among patients hospitalized between March 2020 and October 2021, sixty-eight cases were identified with known underlying rheumatic disease. Seven of these cases were eliminated due to ambiguous data records and 1 was eliminated due to repeated hospitalization. Finaly, 60 patients were considered as the case group. Regarding demographic characteristics based on gender, 60 COVID-19 patients that were hospitalized in the same period but without underlying rheumatic diseases, were selected randomly as control group. All clinical and laboratory measures of the patients upon admission were collected from their documents in the hospital data record system. The analysis of lung images of the patients upon admission were carried out in collaboration with the pulmonology department of the hospital. The estimate of lung involvement percentage was performed based on published methods [19].

All recorded variables were imported to R version 4.1.2 and SPSS statistics 26 for analysis. The difference significance among quantitative variables were measured with Student's t-test. Thus, the correlation of quantitative variables

was shown by calculating Pearson's Correlation Coefficient (r). Furthermore, Fisher's exact test and the chi-squared test were used to determine the significance of the variance in qualitative measure frequencies. The association of qualitative data were measured by odds ratio (CI 95%). A P-value below 0.05 were considered as significant in statistical tests. All data visualization was performed with the R package ggplot2.

This study was approved by the national committee of ethicsof the Iran University of Medical Sciences (approval code IR.IUMS. FMD.REC.1399.528). Informed consent was obtained from all subjects and/or their legal guardian(s). At the time of enrollment, every member of the study population consented to the collection of their clinical data for future use as their medical history and potentially for research and educational reasons. All procedures were carried out in conformity with the applicable rules and regulations.

Results

Demographic and clinical comparison between case and control groups

Sixty COVID-19 patients with rheumatic diseases (case group) and 60 COVID-19 patients without known rheumatolic diseases (control group) were enrolled in the study. Undrlying rheumatic disease in the case group were rheumatoid arthritis (RA) in 32 (53%), systemic lupus erythematosus in 11 (18%), scleroderma in 4 (7%), Behçet's disease in 4 (7%), granulomatosis with polyangiitis in 4 (7%), psoriatic arthritis in 2 (3%), anti-phospholipid syndrome in 1 (0.16%), dermatomyositis in 1 (0.16%) and sarcoidosis in 1 (0.16%) patients. The case and control groups were matched for sex. The average age of the case group was 53.7 (with a maximum age of 85 and a minimum age of 21), whereas the average age of the control group was 57.9 (with a maximum age of 92 and a minimum age of 23).

In the case group, in addition to the underlying rheumatic disease, 30 patients had at least one comorbidities including, HTN, cardiovascular diseases, diabetes mellitus and malignancies. Hence, in control group, 30 patients experienced such a comorbidities. So, the case and control groups were similar based on comorbidities except the rheumatic disease.

Regarding COVID-19 treatment, there was no significant difference between the case and control groups based on glucocorticoids consumption including, prednisolone, dexamethasone, hydrocortisone (intravenous (IV) or oral) (P-value = 0.43), treatments with antiviral medications including, remdesivir, atazanavir, favipiravir and sofosbuvir (P-value = 0.31), high doses glucocorticoid therapy (125, 250, and 500 mg IV pulses of methyl-prednisolone) (P-value = 0.7), and interferon beta (P-value = 0.67). Comparing two groups according to their treatment with tocilizumab (Actemra) was not statistically feasible in terms of low number of data (1 in case and 3 in control). In general, it can be said that the treatment of COVID-19 was not significantly different between the two groups, so the comparison of COVID-19 prognosis in these two groups is not biased.

We compared a series of laboratory tests between case and control groups (Table 1). The white blood cells (WBC) was not significantly different between case and control groups. In the differentiation of WBCs, the average of neutrophils percentage in case group was not significantly different from the control group. Regarding the percentage of lymphocytes, although a mild lymphocytopenia was evident in both groups, the difference among the groups wasnot statistically significant. There was no significant difference in hemoglobin (Hb) level between the case and control groups. Males and females were divided into two groups and their hemoglobin levels were compared. Females showed a more pronounced difference than men, albeit none of them had a statistically significant difference. Although the number of platelets was lower in the case group compared with control group, this difference was not statistically significant. Moreover, some platelet markers, including platelet cell distribution width (PDW), platelet large cell ratio (PLCR) and mean platelet volume (MPV) were significantly higher in case group (Figure 1). On admission, there was no statistically significant difference between the groups in the results of the liver enzyme tests and renal function tests. LDH level upon admission was not significantly different between case and control groups, although in both groups it was much higher than normal values (Figure 1).

In the investigation of inflammatory markers, in terms of the reporting of C-reactive protein (CRP) level as a range (> 6, > 12, > 24, > 48)

Table 1. Comparison of laboratory and clinical measures upon admission between case and control groups. Asterisks indicate statistical significance.

	Case (mean)	Control (mean)	P-value
WBC (*1000/mm³)	7.31	7.10	0.77
Neutrophils %	80.43	78.47	0.3
Lymphocyte %	14.04	16.76	0.12
Hb (g/dl)	11.85	12.43	0.14
Hb (female)	11.57	12.28	0.11
Hb (male)	12.54	12.82	0.74
PLT (*1000/mm³)	173.90	193.27	0.21
PDW (Fl)	13.07	11.85	0.007 *
PLCR (%)	25.75	22.21	0.004 *
MPV (FL)	9.95	9.45	0.003 *
BUN (mg/dl)	19.27	18.90	0.88
Cr (mg/dl)	1.76	1.3	0.16
AST (IU/L)	74.26	63.36	0.39
ALT (IU/L)	62.14	52.43	0.4
LDH (IU/L)	764.96	779.93	0.83
CRP	3.46	3.42	0.84
ESR (mm/hr)	57.02	47.86	0.056
ESR (female)	60.50	45.24	0.03 *
ESR (male)	48.20	47.07	0.91
CPK (U/L)	148.6	309.26	0.04 *
Albumin (g/dl)	3.28	3.51	0.056
Lung %	47.39	48.82	0.76

and not an exact number, for statistical analysis purpose the values < 6 were considered as 1, 6-12 as 2, 12- 24 as 3, 24-48 as 4 and values > 48 were considered as 5. The average level in case and control groups were not significantly different. On the other hand, erythrocyte sedimentation rate (ESR) level in the case group was higher than the control group with a P-value close to significance cutoff. This tendency was mainly in terms of the difference in the ESR level of females (Figure 1). The average maximum normal value of ESR defined by the laboratory in males and females was 15 mm/hr and 20 mm/hr, respectively. The Albumin showed a tendency to ward higher levels (and closer to normal) in control group. Additionally, the control group's creatine phosphokinase (CPK) level was much greater (Figure 1). Ferritin, D-dimer,troponin, and IL6 statistical analysis was not carried out for these variables due to inadequate data. Thus, the lung involvement percentage based in the first image upon admission including, chest computed tomography (CT) scan and chest X-ray showed no significant difference between case and control groups.

Clinical outcomes comparison in case and control groups

Hospitalization time, intensive care unit (ICU) admission, and death were used to gauge the clinical outcome in COVID-19 patients with or without underlying rheumatic illnesses. Hospital stays lasted an average of 10.03 days in the case group and 9.72 days in the control group, with no statistically significant difference between the two groups (P-value = 0.85). 16 patients in the case and 21 patients in control group were admitted to ICU in their treatment procedure, which was not considered different statistically (OR = 0.67, P-value = 0.43). The difference in the mortality rate in the case group (13 patients) and the control group (15 patients) was not significant (OR = 0.83, P-value = 0.83). The association of variables, such as lactic dehydrogenase (LDH), CPK, hemoglobin (Hb),

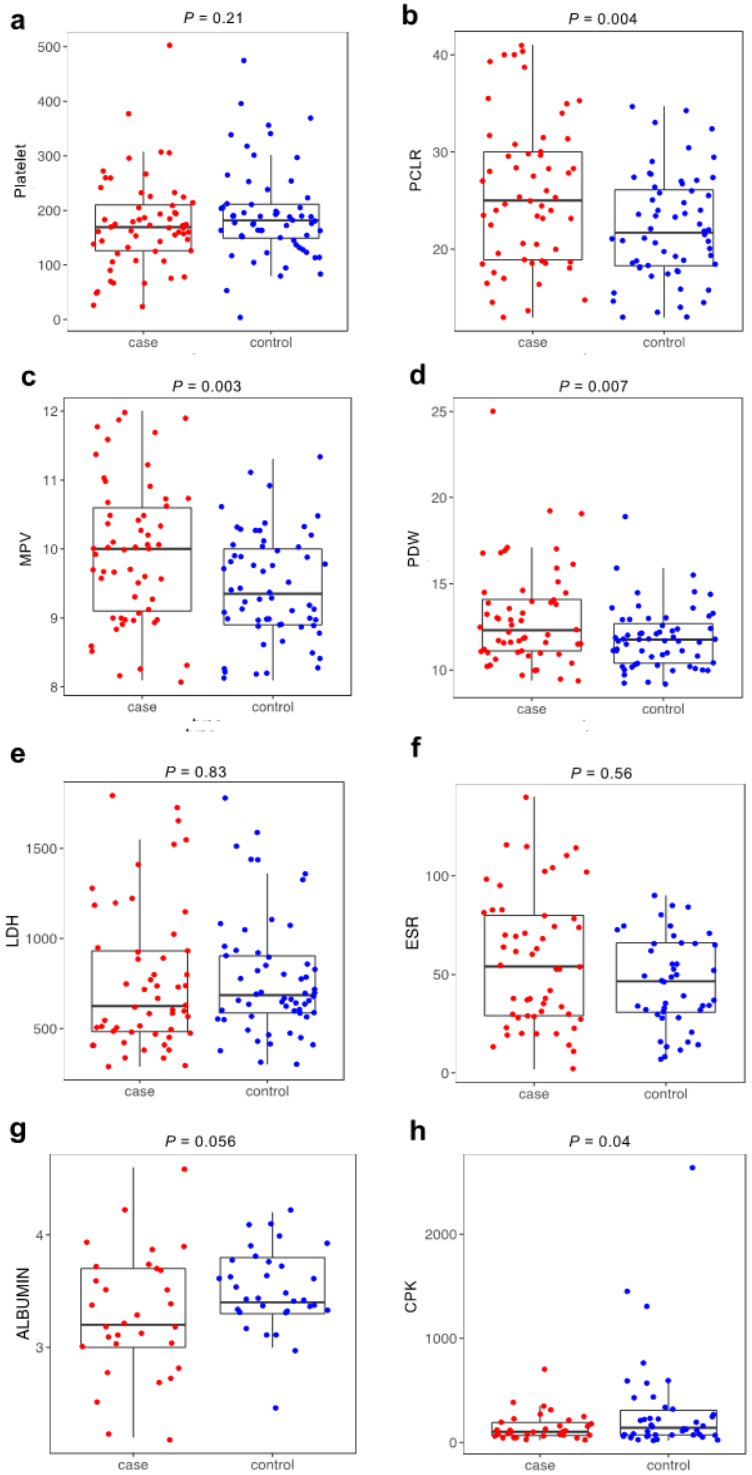

Figure 1. Comparison of laboratory measures upon admission between case and control groups (See Table 1 for full list of measures compared)

lymphocyte count, platelet count, platelet markers, ESR and percentage of lung involvement upon admission with clinical outcome criteria was measured for all COVID-19 patients (total), and separately in the case and control groups (Table 2). The hospitalization duration was associated with percentage of lung involvement upon admission in case and total patients' groups and not in the control group. Furthermore, the hospitalization duration showed amild and still significant association with LDH level in case group. Other measured variables showed no association with hospitalization duration neither in case nor

Table 2. The analysis of association between laboratory and clinical measures with clinical outcome in case, control and total patients groups. Asterisks indicate statistical significance.

	Hospitalization duration						ICU Admission			Mortality		
	total		case		control		total	case	control	total	case	control
	r	P	r	P	r	P	P	P	P	P	P	P
LDH	0.13	0.15	0.3	0.03 *	-0.11	0.41	0.0008 *	0.00005 *	0.91	0.004 *	0.005 *	0.36
CPK	0.02	0.82	0.18	0.31	-0.01	0.94	0.79	0.09	0.63	0.32	0.13	0.65
PLT	-0.05	0.58	-0.02	0.89	-0.09	0.48	0.64	0.59	0.21	0.7	0.31	0.19
PLCR	-0.02	0.79	-0.01	0.92	-0.07	0.58	0.65	0.8	0.93	0.36	0.42	0.57
MPV	-0.08	0.4	-0.09	0.52	-0.09	0.47	0.77	0.98	0.91	0.53	0.74	0.49
PDW	-0.02	0.79	-0.02	0.9	-0.07	0.6	0.92	0.74	0.66	0.4	0.28	0.83
Hb	0.08	0.38	-0.01	0.91	0.22	0.09	0.6	0.3	0.09	0.5	0.13	0.61
ESR	-0.14	0.16	-0.14	0.32	-0.15	0.34	0.31	0.45	0.004 *	0.46	0.97	0.17
Lym %	-0.08	0.42	0	0.97	-0.15	0.28	0.17	0.85	0.04 *	0.54	0.52	0.12
Lung %	0.24	0.02 *	0.3	0.04 *	0.19	0.17	0.00005 *	0.003 *	0.005 *	0.001 *	0.002 *	0.05 *

Table 3. The analysis of association between hospitalization duration, ICU admission, age and gender with mortality in case, control and total patients groups. Asterisks indicate statistical significance.

		total	case	control
Hospitalization duration (days)	Survivors	8.27	8.08	8.46
	Non-survivors	15.14	17.08	13.46
	P-value	0.01 *	0.08 *	0.06
ICU admission	P-value	9.12E-11 *	6.23E-7 *	9.35E-5 *
Age	Survivors	53.09	50.72	55.55
	Non-survivors	64.64	64.31	64.93
	P-value	0.0007 *	0.005 *	0.059
Gender	P-value	0.22	0.21	0.86

control group. ICU admission was highly associated with the percentage of lung involvement upon admission in case (P-value = 0.003), control (P-value = 0.005) and total patients (P-value = 0.00005) groups. Further ICU admission was associated with LDH in case (P-value = 0.00005) and total patients (P-value = 0.0008) (Figure 2), and with ESR and lymphocyte percentage only in control group. The mortality rate, like other clinical outcome criteria, was associated with lung involvement upon admission in case (P-value = 0.002), control (P-value = 0.05), and total patients (P-value = 0.001) groups. Besides, the mortality rate was associated with LDH level in case (P-value = 0.005) and total patients (P-value = 0.004) groups and not in control group (Figure 2). Such an association was not observed between mortality rate and other variables.

Furthermore, in case, control, and total patient groups (Table 3), the relationship between two other outcome criteria (hospitalization length and ICU admission), as well as age and gender, was assessed. Although the association between mortality and hospitalization duration passed the statistical significance level only in total patients group (P-value = 0.01), its association with ICU admission was clear in all three groups i.e. case (P-value = 6.23E-27), control (P-value = 9.35E5), and total patients (P-value = 9.12E-11). Of note, although no significant association between mortality rate and gender was observed, it was seen with patient's age.

Then, we calculated Odds ratio (OR) of

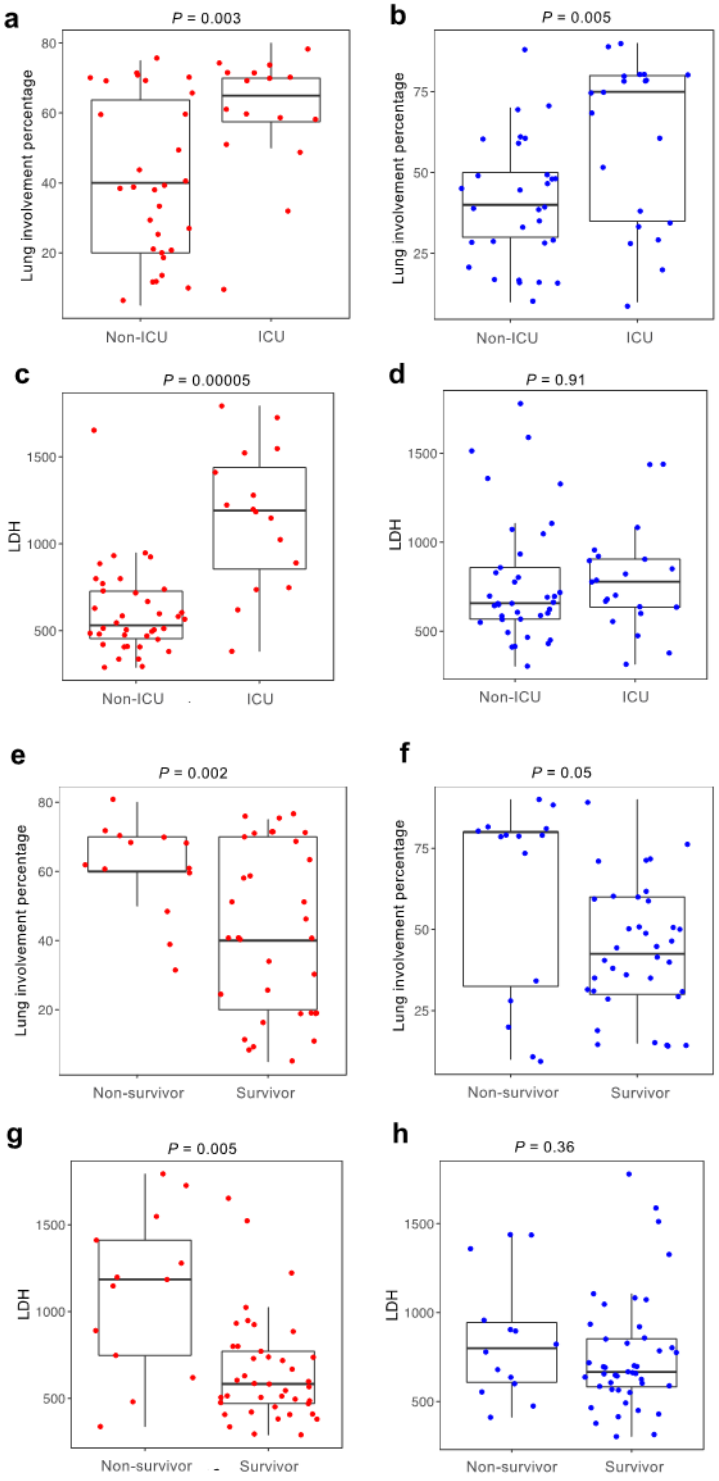

Figure 2. The association between lung involvement percentage and LDH level with ICU admission and mortality in case and control groups. The left column (a, c, e and g panels) refer to case group and the right column (b, d, f and h panels) indicate the control group.

mortality in case and control groups for different factors i.e. gender, age over 65 and ICU admission. OR for male gender in case and control group was 2.75 and 1.37, respectively. Although this was higher in case than control group, none were statistically significant (P-value = 0.16 and 0.74 in case and control groups, respectively). OR for age over 65 was 4.06 (P-value = 0.05) in case and 2.37 in control group (P-value = 0.2), showing a tendency toward

significance only in case group. On the other hand, the OR for ICU admission was relatively high in both case (41.01) and control (15.03) groups. In addition, we calculated the OR of mortality in the case group for other underlying diseases i.e. HTN, ischemic heart disease (IHD) and previous cancer. OR for HTN, IHD and cancer were 1.8, 6.24 and 1.85, respectively. Considering low prevalence in the study population, such a calculation was not performed for diabetes mellitus and ESRD. Thus, the association between the mortality rate and treatment with anti-rheumatic drugs was calculated. The findings indicated that there was no correlation between mortality and prednisolone dose < 10 mg/d (OR = 1.04, P-value = 1). The impact of biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) therapy was consistent with the trend toward greater mortality seen with conven-tional synthetic DMARD (csDMARD) (OR = 2.3), which was not statistically significant (P-value = 0.48). Finally, although immunosuppressants with an OR of 0.16 suggested a potential protective effect, this was not statistically significant (P-value = 0.08) (Figure 3a). In

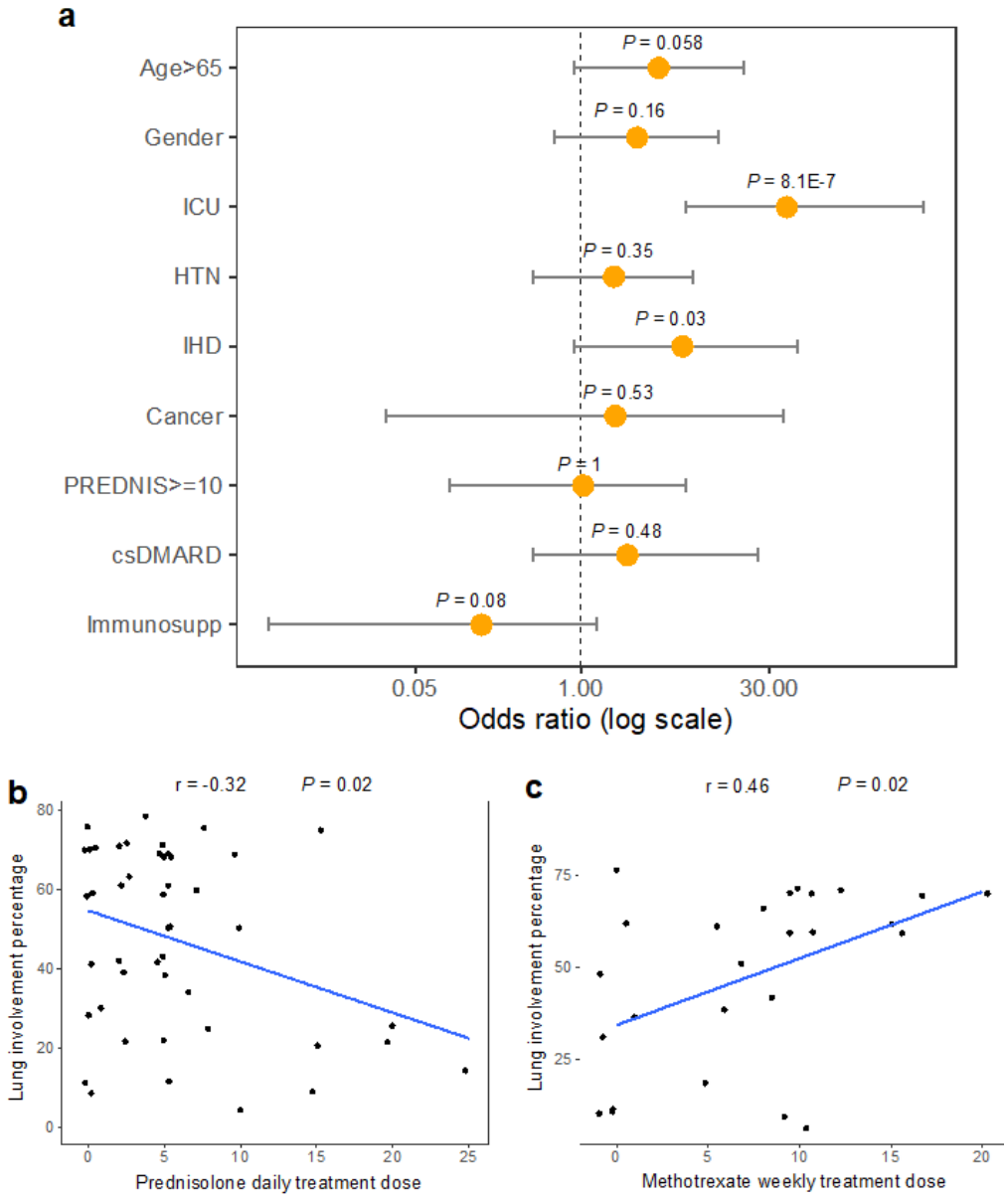

Figure 3. The analysis of possible COVID-19 risk factors in case group. a) The odds ratio and P-value of factors for COVID-19 mortality. b and c) Correlation between Prednisolone daily treatment dose and methotrexate weekly treatment dose with percentage of lung involvement upon admission.

addition, there was a weak negative correlation (r = -0.32, P-value = 0.02) between the daily prednisolone dosage and the proportion of lung involvement (Figure 3b). Therefore, even though it was unrelated to ICU admission and death, the patients who were getting greater doses of prednisolone had less lung involvement when they were first admitted. Furthermore, in the RA patients, the association between weekly methotrexate (MTX) dose and percentage of lung involvement, ICU admission and mortality was measured. Although MTX dose was not associated with ICU admission (P-value = 0.74) and mortality (P-value = 0.56), it was positively correlated with lung involvement percentage (r = 0.46, P-value = 0.02) (Figure 3c).

Discussion

To test the hypothesis that whether patients with underlying chronic rheumatic diseases experience a more severe COVID-19, the population of these patients, although a limited number, that was hospitalized (case) were compared with a control group that were matched for gender, age and other underlying non-rheumatic diseases. These matched factors are reported to be risk factors for increased severity and mortality of COVID19 [20]. As stated, the clinical outcome was compared between case and control groups using three criteria: hospitalization duration, ICU admission, and mortality. In our research, we found no significant correlation between rheumatic diseases and any of these factors. Consistent with our results, in other studies [21], this measurement for the mortality of rheumatic patients (compared with general population) resulted in an OR of 1.69 and 1.1 [22, 23]. In another study, comparing COVID-19 patients with or without rheumatic disease from the same hospital, resulted in an OR of 1.02 for the association between rheumatic disease and mortality [24]. Yet, in another study OR was 1.08 [25]. OR for the association between rheumatic disease, and ICU admission in two latter mentioned studies were 1.32 and 1.27, respectively. Furthermore, we measured such risk only for rheumatoid arthritis patients which resulted in an OR = 1.11 (P-value = 0.82), comparable with a similar study reporting an HR of 1.35 [5].

In addition to results, case and control groups were compared for clinical and laboratory parameters that were risk factors for the severity of the condition. Numerous clinical and laboratory tests have been used to estimate COVID-19 severity. For example it was reported that in general the increase in LDH, CRP, AST, ALT, CPK, D-dimer, IL6, ESR and decrease in lymphocytes, Albumin and Hb were risk factors predictive of disease severity [26]. In another study, age, lymphocyte to leucocyte ratio, CRP, O2 saturation and underlying diseases were counted as COVID-19 severity risk factors and based on these factors, the patients were categorized in low, moderate and high risk groups [27]. Hence, among the biomarkers and cytokines affecting COVID-19 severity, high levels of IL10, IL6, CRP and LDH were significantly associated with the disease severity [28]. Therefore, we compared the levels of LDH, CPK, platelet, lymphocyte percentage, Hb and ESR as disease severity markers between case and control groups. The COVID-19 severity is not different between the case and control groups based on these criteria, with the exception of CPK, which was greater in the control group and albumin, which was marginally lower in the case group. We showed that percentage of lung involvement upon admission was not different between case, and control groups. A greater LDH level was substantially related with a bad result in the case group (and not in the control group), according to the relationship between laboratory measurements and clinical outcome that was assessed separately for the case and control groups. Higher percentage of lung involvement was significantly associated with poor outcome in both groups, so the percentage of lung involvement upon admission compared tolaboratory measures is more certain in initial evaluation of COVID-19 patients. Regarding the platelet markers, higher levels of PDW, PLCR and MPV in severe cases of COVID-19 and non-survivors compared to survivors was reported [18]. These indicators of younger platelets have been demonstrated to be considerably greater in COVID-19 patients compared to non-COVID-19 controls, and they are thought to be able to predict COVID-19 mortality [29]. Also, in our study, all these three markers were significantly higher in case group. However, no significant association between these markers and clinical outcomes were found in neither groups.

Several studies suggested older age as a risk

factor for COVID-19 severity [2, 27]. Our results consistent to these reports showed a significant association between older age and mortality in both groups. Some reports suggest male gender as a risk factor for ICU admission and mortality in COVID-19 [30]. In our analysis, there was a trend toward this link between male gender and mortality, although it was not statistically significant (case group OR = 2.75 and control group OR = 1.37). As females constituted most of the population in our study (only 28% males), it could be possible that such measures on larger population would lead to more significant results. Besides, different studies reported some underlying diseases and previous daily prednisolone dose as COVID-19 severity risk factors in patients with rheumatic diseases. For example, age > 65, prednisolone dose > 5-10 mg/ d, underlying diseases, such as cardiovascular, pulmonary, and chronic renal diseases, HTN, diabetes mellitus and ESRD and male gender were shown to be associated with longer hospitalization duration and increased mortality, while some reports suggest that previous usage of DMARD, lower prednisolone doses and male gender were not associated tohospitalization in these patients [9, 31-33]. Age > 65, male gender, other underlying disorders such HTN, IHD, and prior cancer, as well as the use of cs-DMARD, were linked to COVID-19 mortality in our research in the case group, albeit this connection was statistically significant only for age > 65 and IHD. However, no association was observed for daily Prednisolone does > 10 mg (OR = 1.04). Moreover, Prednisolone and MTX dose showed no association with mortality rate in the case group.

Conclusions

To conclude, based on our results, there is no significant association between rheumatic diseases, and poor COVID-19 clinical outcomes relative to other patients, so these patients are not at clinical risk in this regard. In both case and control groups, older age and a larger proportion of lung involvement were linked to increased mortality.

Although there was a trend for men to have worse outcomes, this difference was not statistically significant. LDH level was the only laboratory measure that was associated to poor clinical outcome in COVID-19 patients with rheumatic disease and not the control group Moreover, the platelet size markers known as COVID-19 severity factors according to previous reports, were all higher in case group, although it was not associated with poorer clinical outcome. Finally, in case group, age > 65 and IHD are significantly associated with higher COVID-19 mortality. There was no association or tendency between high daily dose of Prednisolone and mortality in COVID-19 patients with rheumatic disease. Finally, we suggest data collection from more patients in several centers in future studies for more robust conclusions.

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Conflict of Interest

All authors declare that they have no conflict of interest.

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No found.

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