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Autoimmune Diseases in Patients Hospitalized with COVID-19

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ABSTRACT

Introduction: The aim of this study is to determine the course of COVID 19 in patients with autoimmune diseases (AD), and to investigate the severity of disease, need for intensive care and mortality in these patients.

Methods: In this study, 125 patients who had COVİD-19 and were diagnosed with autoimmune disease before, were evaluated retrospectively. Comorbidities, demographics, laboratory findings, rates of mortality, intensive care unit admission, administration of immunosuppressive treatments and length of hospital stay were collected.

Results: All patients had a positive SARS-CoV-2 PCR test. The most common autoimmune diseases were rheumatoid arthritis, Hashimoto's thyroiditis and inflammatory bowel diseases.

Aiscussion And Conclusion: Our results have shown diabetes mellitus (DM), neutrophil lymphocyte ratio and platelet count were found to be an independent risk factor for mortality in patients with AD.

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Introduction

COVID-19 is a respiratory infection with symptoms. Although most patients experience the disease asymptomatically, some patients develop acute respiratory distress syndrome, which leads to death[1].

Autoimmune diseases are characterized by complement activation and systemic inflammation caused by autoantibodies[2]. Immunosuppressive drugs form the basis of treatment in these patients[3]. It has been considered in some studies that use of immunosuppressive drugs and the inappropriate immune response may increase susceptibility to COVID 19 and the severity of the disease [4,5].

Some studies show that immunosuppression has a protective effect against COVID 19, on the contrary, other studies confirmed that baseline immunodeficiencies increase the severity of the disease [6,8]. There were not enough comprehensive studies on the conditions that affect the prognosis in autoimmune diseases. Our aim in this study is to evaluate the prognosis of COVID 19 in patients with autoimmune disease.

Material And Method

In this retrospective cohort study, 648 patients over 18 years of age, who were admitted to the Ankara City Hospital, Internal Medicine inpatient clinic between July 1 and December 31, 2020 due to COVID-19 were evaluated for eligibility. 125 patients who were previously diagnosed with autoimmune disease and hospitalized for covid were included. Diagnosis of COVID-19 was confirmed with a reverse transcription polymerase chain reaction (RT-PCR) test from nasopharyngeal swab. Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 28/05/ 2020, Number: E1-20-674).

Comorbidities, demographics, laboratory findings, rates of mortality, intensive care unit admission, administration of immunosuppressive treatments and length of hospital stay were recorded. Mortality, intensive care unit (ICU) admission, length of hospital stay were set as outcome measures. All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole). Ethical approval and permission from the Ministry of Health was obtained.

Statistical analysis was made by Statistical Package for Social Sciences version 26. Normality of variables was analyzed by Shapiro-Wilk test. Continuous variables were expressed either as mean ± standard deviation or as median and minimum-maximum values according to normality.

For comparison of continuous variables according to normality, the Mann–Whitney-U test or the Student's t-test was utilized.. The Pearson's χ2test and Fisher's final test were used to evaluate categorical variables. Multivariate logistic regression analyses were performed to determine the factors related to mortality. The p-values <0.05 were considered statistically significant.

Results

125 patients were included in this study. Comparative clinical and laboratory characteristics of patients were presented in Table 1. A significant difference was observed between age, diagnosis of diabetes, Typical involvement on Computed Tomography (CT), need for intensive care and length of stay by comparing the deceased and survivor groups ($p<0.05$). White blood cell, neutrophil, neutrophil lymphocyte ratio, platelet, C- reactive protein, procalcitonin, lactate dehydrogenase, fibrinogen, d-dimer, ferritin values which measured at 24th hour were significantly higher in the deceased group ($p<0.05$). Lymphocyte levels were significantly higher in the survivor group ($p<0.05$).

Comparative autoimmune disease characteristics in deceased and survivor groups were presented in Table 2. The most common autoimmune diseases were rheumatoid arthritis (%31.2), Hashimoto's thyroiditis (%26.4) and inflammatory bowel diseases (%8.8), respectively. The most commonly used drugs in patients treated for autoimmune disease were prednisolone (24%), hydroxychloroquine (17.6%) and methotrexate (9.6%), respectively. There was no significant difference between the two groups in terms of autoimmune diseases or the immunosuppressive drugs used in the treatment.

Univariate and multivariate regression analysis for mortality were presented in Table 3. In the performed univariate analysis, a significant relationship was found in terms of age (Odds ratio (OR) for the risk of mortality; 1.053 (1.017-1.090), $p<0.05$, 95% confidence interval [CI]), diabetes mellitus (OR; 4.094 (1.730-9.687), $p<0.001$, 95% CI), white blood cell (OR; 1.179 (1.049-1.326), $p<0.05$, 95% CI), neutrophil (OR; 1.328 (1.145-1.540), $p<0.001$, 95% CI), neutrophil lymphocyte ratio (OR; 1.097 (1.042-1.155), $p<0.001$, 95% CI), platelet (OR; 1.006 (1.001-1.011), $p<0.05$, 95% CI), crp (OR; 1.009 (1.004-1.014), $p<0.05$, 95% CI), fibrinogen (OR; 1.449 (1.137-1.847), $p<0.05$, 95% CI) and ferritin (OR; 1.001 (1.000-1.001), $p<0.05$, 95% CI) for the risk of developing mortality, respectively.

In the performed multivariate analysis, a significant relationship was found in terms of diabetes mellitus (OR; 7.435 (2.540-21.759), p<0.001, 95% CI), neutrophil lymphocyte ratio (OR; 1.102 (1.045-1.163), p<0.001, 95% CI), platelet (OR; 1.008 (1.002-1.014), p<0.05, 95% CI) for the risk of developing mortality, respectively.

Diabetes mellitus, neutrophil lymphocyte ratio and platelet levels were found to be independent risk factors for mortality. The negative predictive value was 84.7 for diabetes (OR for the risk of mortality; 4.1 (1.7-9.7), 95% CI), 86.4 for neutrophil lymphocyte ratio (OR; 4.8 (2.0-11.5), 95% CI) , and 89.1 for platelet (OR; 4.3 (1.6-11.4), 95% CI), respectively.

Predictive values of independent risk factors for mortality were presented in Table 4. The sensitivity and specificity for the risk of developing mortality were 56.7 and 75.8 for diabetes, 63.3 and 73.7 for neutrophil lymphocyte ratio and 80.0 and 51.6 for platelet, respectively. The AUC (Area Under the Curve) of DM (diabetes mellitus), NLR (neutrophil lymphocyte ratio) and platelet for mortality was presented in Figure 1.

Discussion

In this study, we report the comorbidities, laboratory findings and outcomes of 125 COVID-19 patients with autoimmune diseases. Comorbidities such as diabetes mellitus and hypertension are important risk factors for the disease severity and mortality in patients with COVID-19 (9). Our study demonstrated that patients who had diabetes mellitus were seen to have a higher risk for mortality due to COVID-19.

In this study, we retrospectively analyzed the comorbidities, effect of the treatment for AD and laboratory findings of 125 COVID-19 confirmed patients with AD. In our study no significant correlation was found between autoimmune diseases and treatment regimens in terms of mortality. We find that DM, NLR and platelet levels increase the risk of mortality in patients with AD. In most studies, similar to our study, pre-existing comorbidities were shown to be associated with higher severity and mortality in these patients. However, autoimmune diseases were not an independent prognostic factor[10,11]. NLR levels remained significantly higher in the deceased group. Similar to our study; Seyit M et al. found that NLR levels were higher in COVID-19 patients in their study and Yang et al. reported NLR levels were significantly higher in severe patients[12,13]. In our study, patients with thrombocyte levels above 193.5 10^9/L had an increased risk of mortality in contrast to our study, some studies revealed a correlation between thrombocytopenia and disease severity, also mortality[14].

Conclusion

We found that NLR and platelet levels are independent risk factors for mortality in patients with autoimmune disease, independent of the development of thrombocytopenia, unlike the normal population diagnosed with COVID-19.

Our study had several limitations. Firstly, we had a small sample size. In addition, autoimmune disease activity in these patients and the effect of treatments used for the disease were not included in the study. Therefore, comprehensive studies should be conducted in a larger cohorts by evaluating disease activity and treatment regimens.

Table 1. Comparative clinical and laboratory characteristics				
Parameters	**Overall population N=125**	**Deceased group N=30**	**Survivor group N=95**	***P* value**
Age, years (mean ± SD)	63.34 ± 13.95	70.00 ± 9.51	61.24 ± 14.50	<0.001
Gender				0.334
Female	72 (57.6%)	15 (50.0%)	57 (60.0%)	0.334
Male	53 (42.4%)	15 (50.0%)	38 (40.0%)	0.334
Comorbidity (other than rheumatic disease)				
Coronary artery disease	39 (31.2%)	13 (43.3%)	26 (27.4%)	0.100
Hypertension	78 (62.4%)	22 (73.3%)	56 (58.9%)	0.156
Diabetes mellitus	40 (32%)	17 (56.7%)	23 (24.2%)	0.001
Other	62 (49.6%)	20 (66.7%)	42 (44.2%)	0.032
Typical involvement on CT	103 (82.4%)	30 (100%)	73 (76.8%)	0.004
Intensive care unit admission	43 (34.4%)	27 (90%)	16 (16.8%)	<0.001
Length of stay (days)	11 (7-17.5)	16 (8-26)	10 (7-16)	0.046
Mortality	30 (24.0%)	-	-	-
Laboratory findings* (24th hour)				
White blood cell (10^9/L)	5.92 (4.26-8.37)	8.71 (5.22-10.54)	5.69 (4.11-7.64)	0.001
Neutrophil (10^9/L)	4.58 (2.47-6.95)	7.41 (3.97-9.42)	3.78 (2.31-5.97)	<0.001
Lymphocyte (10^9/L)	0.87 (0.55-1.25)	0.66 (0.4-0.95)	0.9 (0.61-1.28)	0.015
Neutrophil lymphocyte ratio	5.11 (2.46-9.72)	8.73 (4.72-19.34)	4.25 (1.94-8.17)	<0.001
Hemoglobin (g/dL)	12.53 ± 1.92	12.22 ± 2.00	12.63 ± 1.90	0.319
Platelet (10^9/L)	217.60 ± 88.28	251.77 ± 101.25	206.81 ± 81.42	0.014
C- reactive protein (mg/L)	43 (14.5-127)	112.5 (41.25-179)	33 (10-84)	<0.001
Procalcitonin (µg/L)	0.06 (0.03-0.2)	0.19 (0.08-0.74)	0.05 (0.03-0.12)	<0.001
Lactate dehydrogenase (U/L)	336 (259.5-481)	503.5 (306.5-623.5)	324 (242-406)	<0.001
Fibrinogen (g/L)	4.65 ± 1.76	5.53 ± 1.92	4.38 ± 1.63	0.002
D-dimer (mg/L)	0.8 (0.42-1.7)	1.23 (0.69-2.55)	0.75 (0.4-1.2)	0.002
Ferritin (µg/L)	277 (121-594.5)	469 (259-1218.5)	218 (110-499)	0.001

Tablo 2. Comparative autoimmune disease characteristics in deceased and survivor				
Parameters	**Overall population N=125**	**Deceased group N=30**	**Survivor group N=95**	***P* value**
Hashimoto's thyroiditis	33 (26.4%)	9 (30%)	24 (25.3%)	*0.608*
Connective tissue disease				
Rheumatoid arthritis	39 (31.2%)	11 (36.7%)	28 (29.5%)	0.459
Sjogren's syndrome	5 (4%)	2 (6.7%)	3 (3.2%)	0.593
Systemic lupus erythematosus	3 (2.4%)	-	3 (3.2%)	1.000
Scleroderma	2 (1.6%)	2 (6.7%)	-	0.056
Dermatomyositis	1 (0.8%)	-	1 (1.1%)	1.000
Other				
Behcet's disease	5 (4%)	-	5 (5.3%)	0.336
Ankylosing spondylitis	7 (5.6%)	1 (3.3%)	6 (6.3%)	1.000
Familial mediterranean fever	4 (3.2%)	2 (6.7%)	2 (2.1%)	0.243
Multiple sclerosis	4 (3.2%)	-	4 (4.2%)	0.572
Immune thrombocytopenic purpura	3 (2.4%)	2 (6.7%)	1 (1.1%)	0.143
Inflammatory bowel disease	11 (8.8%)	3 (10%)	8 (8.4%)	0.724
Psoriasis	7 (5.6%)	1 (3.3%)	6 (6.3%)	1.000
Celiac disease	1 (0.8%)	-	1 (1.1%)	1.000
Sarcoidosis	1 (0.8%)	-	1 (1.1%)	1.000
Immunoglobulin A nephropathy	1 (0.8%)	-	1 (1.1%)	1.000
Primary sclerosing cholangitis	2 (1.6%)	-	2 (2.1%)	1.000
Primary biliary cholangitis	1 (0.8%)	-	1 (1.1%)	1.000
Antiphospholipid antibody syndrome	1 (0.8%)	-	1 (1.1%)	1.000
Myasthenia gravis	6 (4.8%)	2 (6.7%)	4 (4.2%)	0.629
Guillain-barre syndrome	1 (0.8%)	-	1 (1.1%)	1.000
Pemphigus vulgaris	1 (0.8%)	-	1 (1.1%)	1.000
Immunosuppressive drug use				
Prednisolone	30 (24%)	6 (20%)	24 (25.3%)	0.556
Hydroxychloroquine	22 (17.6%)	6 (20%)	16 (16.8%)	0.692
Sulphasalazine	7 (5.6%)	3 (10%)	4 (4.2%)	0.357
Methotrexate	12 (9.6%)	4 (13.3%)	8 (8.4%)	0.480
Leflunomide	7 (5.6%)	2 (6.7%)	5 (5.3%)	0.673
Azathioprine	9 (7.2%)	3 (10%)	6 (6.3%)	0.447
Mycophenolate	5 (4%)	1 (3.3%)	4 (4.2%)	1.000
Calcineurin_inh	4 (3.2%)	1 (3.3%)	3 (3.2%)	1.000
Colchicine	7 (5.6 %)	1 (3.3%)	6 (6.3%)	1.000
Biological agent	4 (5%)	1 (3.3%)	4 (4.2%)	1.000
Rituximab	1 (0.8%)	-	1 (1.1%)	1.000

Table 3. Univariate and multivariate regression analysis for mortality				
	Univariate analysis		**Multivariate analysis***	
Parameters	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age	1.053 (1.017-1.090)	0.004		
Diabetes mellitus	4.094 (1.730-9.687)	0.001	7.435 (2.540-21.759)	<0.001
White blood cell (10^9/L)	1.179 (1.049-1.326)	0.006		
Neutrophil (10^9/L)	1.328 (1.145-1.540)	<0.001		
Lymphocyte (10^9/L)	0.851 (0.506-1.431)	0.543		
Neutrophil lymphocyte ratio	1.097 (1.042-1.155)	<0.001	1.102 (1.045-1.163)	<0.001
Hemoglobin (g/dL)	0.895 (0.721-1.112)	0.317		
Platelet (10^9/L)	1.006 (1.001-1.011)	0.018	1.008 (1.002-1.014)	0.008
C- reactive protein (mg/L)	1.009 (1.004-1.014)	0.001		
Procalcitonin (µg/L)	1.084 (0.914-1.286)	0.354		
Lactate dehydrogenase (U/L)	1.001 (1.000-1.002)	0.073		
Fibrinogen (g/L)	1.449 (1.137-1.847)	0.003		
D-dimer (mg/L)	1.048 (0.910-1.206)	0.518		
Ferritin (µg/L)	1.001 (1.000-1.001)	0.031		

Table 4. Predictive values of independent risk factors for mortality							
Parameters	**Cut-off value**	**Number (%) of patients***	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**OR (95% CI)**
Diabetes mellitus	-	40 (32.0)	56.7	75.8	42.5	84.7	4.1 (1.7-9.7)
Neutrophil lymphocyte ratio	7.2	44 (35.2)	63.3	73.7	43.2	86.4	4.8 (2.0-11.5)
Platelet	193.5 10^9/L	70 (56.0)	80.0	51.6	34.3	89.1	4.3 (1.6-11.4)
*Number (%) of patients above or below the given cut-off values. *Abbreviations: PPV; Positive predictive value, NPV; Negative predictive value, OR; Odds ratio, CI; confidence interval.*							

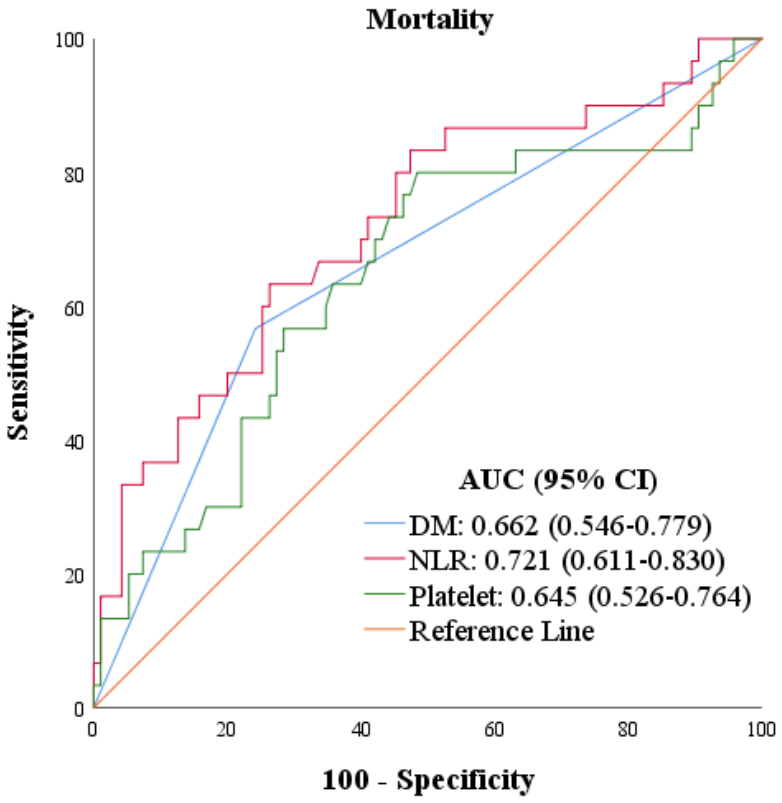

Figure 1. The AUC of DM, NLR and platelet for mortality

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