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The clinical presentation and outcomes of COVID-19 in immunocompromised hosts in comparison to comorbid and immunocompetent patients: retrospective study of 384 cases

Bağışıklığı baskılanmış hastalarda COVID-19'un klinik prezentasyonu ve sonuçları, komorbid ve sağlıklı hastalarla kıyaslama: 384 olgunun retrospektif araştırılması

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ABSTRACT

Aim: Immunocompromised hosts (ICH) are at a higher risk of severe infections and mortality. This study aimed to examine the clinical manifestations and outcomes of ICH who were admitted to the hospital for COVID-19.

Materials and Methods: A total of 384 patients (mean age 61.5±15.9 y, 168 female) who were hospitalized between March 2020 and December 2020 were included in the study. These patients were examined in three groups: the ICH (n=40), comorbid patients (n=101), and the control group comprising immunocompetent patients without any comorbidities (n=243). All clinical and laboratory data were retrieved from the electronic hospital records and compared between the three groups retrospectively.

Results: The mean age was 61.2±15.0 for ICH, 66.1±12.3 for comorbid, and 59.6±17.0 for control groups (p=0.003). We found that the mean leukocyte and neutrophil counts, C-reactive protein (CRP), ferritin, and D-Dimer levels were significantly higher, and the albumin level was lower in ICH compared to the other two groups (p<0.05). On CT scans, ground-glass opacities were seen less frequently in ICH compared to the other groups (p=0.035). The mortality rate was 32.5% in the ICH, 22.8% in the comorbid, and 15.2% in the control groups (p=0.019). Within the ICH group, the mean leukocyte, and neutrophil counts and LDH levels were higher and the $SpO2/FiO_2$ ratio was lower in patients who died (p<0.05).

Conclusion: We found that had higher mortality in ICH with COVID-19. Being ICH condition, elder age, elevated LDH levels, and decreased Sat/FiO2 were associated with increased mortality.

Keywords: Clinical outcomes, COVID-19, immunocompromised, immunosuppressed, pandemic.

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ÖZ

***Amaç**: Bağışıklığı baskılanmış hastalar (BBH) ciddi enfeksiyonlar ve mortalite için yüksek risk taşırlar. Bu çalışma COVİD-19 nedeniyle hastaneye yatırılan BBH'da klinik seyrin ve sonuçların incelenmesini amaçlamaktadır.*

***Gereç ve Yöntem**: Mart 2020 ve Aralık 2020 tarihleri arasında hastaneye kaldırılan 384 hasta (ortalama yaş 61.5±15.9, 168 kadın) çalışmaya dahil edildi. Bu hastalar 3 gruba ayrıldı: BBH (n=40), komorbid hastalar (n=101) ve kontrol grubu olarak immünkompetan hastalar (n=243). Tüm klinik ve laboratuvar verileri elektronik hasta dosyasından alındı ve üç grup karşılaştırıldı.*

***Bulgular**: Ortalama yaş bağışıklığı baskılanmış hastalar için 61.2±15.0, komorbid hastalar için 66.1±12.3, kontrol grubu için 59.6±17.0 olarak hesaplandı. BBH grubunda diğer iki grup ile kıyaslandığında istatistiksel olarak anlamlı şekilde ortalama lökosit ve nötrofil sayısı, C-reaktif protein, ferritin ve D-Dimer düzeylerinin artmış olduğu, albümin seviyelerinin ise azalmış olduğu bulunmuştur (p<0.05). Toraks BT incelemelerinde buzlu cam alanları BBH'da diğer hastalarla kıyaslandığında daha az gözlemlenmiştir (p=0.035). Mortalite oranları BBH grubu için %32.5, komorbid hastalar için %22.8 ve kontrol grubu için %15.2 olarak gözlemlenmiştir (p=0.019). BBH grubunda ölen hastalarda, ortalama lökosit ve nötrofil sayısı ve LDH düzeyleri yüksek iken, SpO2/FiO2 oranı düşük olduğu gözlemlenmiştir (p<0.05).*

***Sonuç**: COVİD-19'lu bağışıklığı baskılanmış hastalarda mortalite oranı daha fazla olarak bulunmuştur. Bağışıklığı baskılanmış olmak, ileri yaş, artmış LDH düzeyleri ve azalmış Sat/FiO2 düzeylerinin mortalite ile ilişkili olduğu gözlemlenmiştir.*

***Anahtar Sözcükler**: Klinik sonuç COVİD-19, bağışıklığı baskılanmış, pandemi.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an upper respiratory infectious disease caused by a Severe Acute Respiratory Syndrome Coronavirus 2 (1). Over 633 million infected cases were reported and over 6.5 million died around the world as of November 2022 (2).

Age, male gender, number of symptoms, respiratory disease, chronic kidney disease, malignancy, transplant history, immunosuppression, and glucocorticoid use have been reported as risk factors for clinical progression and poor outcomes in COVID-19 patients (3–6). There are few studies that have looked into the clinical outcomes of immunocompromised patients with COVID-19.

In this study, we focused to look into the clinical presentations and outcomes in ICH with COVID-19 who were admitted to the hospital.

MATERIALS and METHODS

A total of 384 patients were included in our study who were admitted to the hospital emergency service with COVID-19 symptoms from March 2020 to December 2020, whose COVID-19 PCR test was found to be positive and who were then transferred to the ward. Informed consent was obtained for all patients. Sociodemographic variables, admission symptoms and dates, laboratory results, clinical course, and discharge data were collected.

The clinical course was assessed on an ordinal scale. Thus, clinical progression meant the need for a higher level of treatment, e.g. transfer from the service to the intensive care unit (ICU), changing from no oxygen (O_2) supplementation to O_2 supplementation, from O_2 support to non-invasive mechanical ventilation (NIMV) or from NIMV to intubation and invasive ventilation.

We classified the patients into three groups: the first group contained the immunosuppressed patients; i.e. those who were being followed up for active cancer or were receiving chemotherapy or were solid organ transplant recipients or were regularly using systemic corticosteroids (dosage ≥50mg/day, at least 5 months' usage), biologic agents, and other immunosuppressive drugs, there was not HIV-positive patient in the admission. All patients were evaluated for the need for an ICU and mechanical ventilation by the ICU specialist. Studies showed that diabetes mellitus (DM), chronic kidney disease (CKD), and chronic liver disease (CLD) may cause immune system dysfunction (7–10). Thus, these cases were involved in the second group. The remaining patients had no immunosuppression or comorbidities and were included in the control group.

Statistical Analysis:

Statistical analysis was performed by IBM SPSS 25.0 (Armonk, New York, USA: IBM Corp.®) for Windows packaged software. Numerical

variables were summarized with mean ± standard deviation and categorical variables with percentage and frequency. The significance of differences among groups was assessed with the Student-t Test, Mann-Whitney U or Kruskal Wallis H, ANOVA test, and analysis of categorical variables was examined by Chi-square test. The normality analysis of data was analyzed by the Kolmogorov-Smirnov test. Normally distributed data were analyzed by the ANOVA test and non-normally distributed data were analyzed by the Mann-Whitney U test. A value of *p<0.05* was considered a significance level for all statistical analyses.

Our study got permission from the medical research local ethics committee by approval no: 20-5T/48 in 15.10.2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

RESULTS

All patients admitted to our hospital for COVID-19 during the study period (n=384, 168 female, mean age 61.5±15.9 years), were included.

Forty (10.4%, 13 female) of the patients were immunocompromised and constituted Group 1. Group 2 comprised 101 patients (47 female) with comorbidities (26.3%). Group 3 included 243 control (108 female) patients (63.3%). The mean age was 61.2±15.0, 66.1±12.3, and 59.63±17.0 for the three groups, appropriately (p=0.003).

Of the 40 immunosuppressed cases, 22 were being treated for solid organ tumors, 9 were on regular corticosteroids, 6 had hematologic malignancy, 6 were solid organ transplant recipients, 3 were being treated with biologic agents, 2 were on other immunosuppressive drugs. In Group 2, 88/101 patients had diabetes mellitus (DM), 21/101 had chronic kidney disease (CKD), and 3/101 had chronic liver disease (CLD).

Clinical Presentation and Symptoms

The most common clinical presenting symptoms were dyspnea (n=197, 51%), fever (n=185, 48%), cough (n=180, 47%), fatigue (n=117, 30%), sputum production (n=50, 13%), nausea and vomiting (n=38, 10%). There was no difference in clinical presentation among the three groups.

Laboratory findings

The mean leukocyte, neutrophil counts, C-reactive protein (CRP), ferritin, and D-Dimer levels were elevated, Albumin level was decreased in ICH, p<0.005 among the three groups. While comparing the ICH to the other two groups for these significant parameters, significant differences were found for mean leukocyte count in ICH vs control group with p=0.009, for the mean neutrophil count in ICH vs control with p=0.038, for CRP in ICH vs control with p=0.009, for D-Dimer in both ICH vs comorbid and ICH vs control with p=0.031 and p<0.001 respectively, for Ferritin in both ICH vs comorbid and ICH vs control with p<0.001 and p<0.001, for Albumin in both ICH vs comorbid and ICH vs control with p<0.001 and p<0.001. We did not find significant difference in lymphocyte count, PCT and LDH levels among the three groups (Table-1). The oxygenation levels ($SpO2/FiO_2$ ratio) were also similar (p>0.05).

Radiologic findings

In High-Resolution Computed Tomography (HRCT) imaging, ground-glass opacity (GGO) was seen in 32 (80.0%) ICH patients, in 89 (90.8%) patients with comorbidity, and in 218 (92.8%) control patients (p=0.035). Consolidation was observed in 23 (57.5%), 53 (54.1%), and 103 (43.8%) of the three groups, respectively (p=0.104). Bilateral involvement was found in 32 (80.0%), 91 (93.8%), and 200 (85.1%) cases, in all groups, respectively (p=0.041).

Clinical outcomes and prognosis

During hospitalization, clinical progression was observed in 15 (37.5%) of the ICH, 38 (37.6%) of the patients with comorbidities, and 59 (24.3%) of the controls (p=0.022). With regards to mortality, 13/40 (32.5%) of the ICH, 23/101 (22.8%) of the comorbid patients, and 37/243 (15.2%) of control patients died (p=0.019) (Table-1). On the other hand, we did not observe a significant difference in the requirement for an intensive care unit (p=0.081), the need for NIMV (p=0.086), and for IMV (p=0.196).

When the whole study population was considered, the patients who died were older (72.3±12.3 vs 59.0±15.6 years) (p<0.001). Similarly, the mean age of the patients who died was higher in the comorbid (72.8±13.5 vs 64.1±11.3 years, p=0.003) and control groups (74.7±11.5 vs 56.93±16.4 years, p<0.001). However, within the ICH group, the mean age of the non-survivors and survivors were similar (64.9±9.9 and 59.4±16.8years, respectively, p=0.284).

Table-1. Sociodemographic data, mean laboratory findings, and clinical outcomes comparison between the groups. (The p-value of differences is for the comparison of the three groups.)

Parameters	*Immunocompromised patients, n=40*	*Comorbid patients, n=101*	*Control group patients, n=243*	*p-value*
Age (years)	61.2±15.1	66.1±12.3	59.6±17.0	**0.003**
Male gender, n(%)	27 (67.5)	54 (53.5)	135 (55.6)	0.298
Leukocyte (per µL)	9566.7±9862.3	8006.34±3659.8	7200.3±3649.0	**0.009**
Lymphocyte (per µL)	1899.7±4759.9	1235.2±853.0	1291.1±831.1	0.091
Neutrophil (per µL)	6760.2±5340.2	5819.5±3218.8	5234.3±3446.1	**0.034**
CRP (mg/L)	105.1±86.0	100.8±76.7	68.6±67.9	**<0.001**
PCT (µg/L)	0.25±0.31	0.40±0.76	0.24±0.42	0.432
Ferritin (µg/L)	1673.1±2248.1	568.0±568.3	509.1±507.5	**<0.001**
D-Dimer (µg/L)	2150.0±1542.9	1504.3±1421.8	1207.9±1146.2	**<0.001**
LDH (U/L)	375.6±333.2	340.1±175.2	319.2±152.8	0.247
Albumin (g/L)	33.1±6.3	36.7±4.1	38.2±4.8	**<0.001**
Sat/FiO_2	359.2±104.8	335.5±119.3	364.1±114.3	0.121
Mortality, n (%)	13 (32.5)	23 (22.8)	37 (15.2)	**0.019**
Clinical progression, n(%)	15 (37.5)	38 (37.6)	59 (24.3)	**0.022**

Abbreviations: CRP – C-reactive protein, PCT – Procalcitonin, LDH – Lactate Dehydrogenase, Sat/FiO2 – saturation of oxygen/fraction of inspired oxygen, GGO – Ground Glass Opacity.

Table-2. Mean laboratory findings between survived and dead ICH patients.

Parameters	*ICH who survived n=27*	*ICH who died n=13*	*p-value*
Age (years)	59.4±16.8	64.9±9.9	0.284
Leukocyte (per µL)	5888.5±4141.0	17206.2±13612.2	**<0.001**
Lymphocyte (per µL)	784.4±398.5	4216.2±8042.4	0.057
Neutrophil (per µL)	4598.5±3867.6	11250.0±5283.9	**<0.001**
CRP (mg/L)	92.8±80.8	130.7±94.0	0.161
Ferritin (µg/L)	1312.4±1306.9	2445.9±3561.2	0.647
D-Dimer (µg/L)	1867.4±1388.1	2741.2±1745.9	0.094
LDH (U/L)	274.5±85.8	611.7±542.5	**0.033**
Albumin (g/L)	33.8±6.1	31.7±6.6	0.315
Sat/FiO_2	402.8±85.8	285.2±93.7	**0.001**
GGO	23 (85.2%)	9 (69.2%)	0.237
Consolidation	15 (55.6%)	8 (61.5%)	0.720

Abbreviations: CRP – C-reactive protein, PCT – Procalcitonin, LDH – Lactate Dehydrogenase, Sat/FiO2 – saturation of oxygen/fraction of inspired oxygen, GGO – Ground Glass Opacity.

Within the ICH group, the mean absolute leukocyte (p<0.001) and neutrophil (p<0.001) counts, LDH levels (p=0.032) were higher and SpO2/FiO_2 ratio (p<0.001) was lower in patients who died (Table-2). Within the comorbid group, the mean absolute lymphocyte counts (p=0.006) and CRP levels (p=0.011) were higher and SpO2/FiO_2 ratio (p=0.027) was lower in patients

who died. Comorbid patients who died also had elevated CRP level, we thought that might be caused by a secondary infection. Thus, an increased mean absolute lymphocyte count might result from secondary infection in comorbid patients who died. In our study, the comorbid group did not include the immunocompromised patients, which differs from several studies in the literature. Within the control group, CRP (p=0.001), Ferritin (p=0.013), D-dimer (p=0.002), and LDH levels (p<0.001) were higher, Albumin (p=0.001) and $SpO2/FiO_2$ (p<0.001) ratio was lower in patients who died.

With regards to mortality, 73 (19%) of the study population died and 311 (81%) were discharged. In univariate analysis, the presence of an immunocompromising condition (p=0.019), age (p<0.001), leukocyte (p=0.003), lymphocyte (p=0.024), neutrophil (p=0.001), CRP (p<0.001), PCT (p=0.009), Ferritin (p=0.001), D-dimer (p<0.001), LDH (p<0.001), Albumin (p<0.001), and Sat/FiO2 (p<0.001) were found to be associated with mortality. Multivariate analysis showed that being ICH (p=0.030, 95% CI: 1.130-11.841), older age (p<0.001, 95% CI: 1.055-1.134), and elevated LDH levels (p=0.001, 95% CI: 1.002-1.007) were associated with increased mortality.

There was no difference in the frequency of GGO between the patients who died and those who survived in any of the three groups. Consolidation was more commonly observed in patients who died in the second (78.3% vs 46.7%, p=0.008) and third (59.5% vs 40.9%, p=0.037) groups, but there was no difference in the ICH group (p=0.720).

DISCUSSION

In this study, we aimed to investigate clinical presentations, laboratory findings, HRCT imaging, and clinical outcomes of ICH in comparison to patients with comorbidities and a control group of immunocompetent patients without any chronic disorders. Importantly, mortality was highest in the ICH and the rate of clinical worsening was higher in the ICH and comorbid groups compared with the control patients.

The presenting symptoms were similar among the three groups. It has previously been reported that solid organ transplant recipients may be afebrile and have atypical symptoms at presentation (11–13). The difference in our findings may be related to the degree of immunosuppression; i.e. our study comprised ICH with different etiologies, whereas transplant recipients may have mostly been receiving higher levels of immunosuppressive or anti-rejection therapies.

Akbari et al. showed an increase in leukocyte and neutrophil counts, high levels of CRP, PCT, cytokines, D-Dimer, and decreased lymphocytes and monocyte counts were tightly associated to the severity of COVID-19 (14-15). Similarly, Suárez-Garcia et al. reported that CRP, D-Dimer levels, and leukocyte counts were higher in the ICH compared with non-ICH (16). Neutrophilia has also been observed in patients with the severe clinical course of COVID-19 and activated neutrophils have been thought to contribute to mortality (3), (17–19). In our study, we found elevated CRP, D-dimer, ferritin, and decreased albumin levels in the ICH group, all pointing to a more severe level of inflammation. Besides, although the leukocyte counts were within the normal range in all three groups, the leukocyte and neutrophil counts were significantly higher in the ICH group.

A few studies have looked at the CT findings in the ICH with COVID-19 (20). Sharma et al. found that GGO was the most common pattern, followed by lymphadenopathy and consolidation (21). The study reported that bilateral multilobar consolidations were related to the severity of disease (22). Abrishami et al. showed that ground glass opacity (GGO), the combination of GGO and consolidation, and bilateral involvement were the most common radiologic features and suggestive of poor prognosis in kidney transplanted patients as IMS (20).

In this study, there was a lower rate of ground glass opacities in the ICH compared with the other two groups. Although the difference was statistically significant, it was too small to be of any clinical significance. Similarly, CT findings were not found to be related to the clinical outcome of the ICH group.

The study showed that the prognosis was poorer in the ICH, with higher rates of clinical worsening and mortality. Besides, although older age was related to mortality in the other two groups, there was no difference in age between the patients who died and those who survived; suggesting that immunosuppression is a stronger predictor of outcome compared with age. Besides, within the ICH group, elevated leukocyte, lymphocyte, and

neutrophil counts, and LDH levels were associated with mortality, which may be of use in triaging the ICH for closer follow-up.

Hematologic malignancies and active chemotherapy history had also been related to a poorer prognosis (23). Ward et al. reported that the use of combined immunosuppressive drugs and glucocorticoids were highly associated with an increased death rate, but not with ICU requirements (5). Suárez-Garcia et. al. showed that patients who were treated with immunosuppressive drugs and biological agents, who underwent solid organ transplantation, who had cancer and were hospitalized with COVID-19 had higher mortality than non-immunocompromised patients (16).

Comorbidities were found to be related to poor clinical outcomes in patients with COVID-19 (7), (24), (25). Our study also showed that patients with comorbid conditions had a higher risk of clinical worsening during their hospitalization, but their risk of mortality was not higher like the ICH group. Thus, patients who had comorbidities should be treated as an intermediate risk group with regards to the clinical course of COVID-19.

This study has strengths and weaknesses. The main strength is that it has systematically examined the immunocompromised patients hospitalized with COVID-19 taking into account a wide range of clinical parameters. Another strength is that patients with comorbid conditions were analyzed separately from the ICH and otherwise healthy subjects, which enabled to better define the risk level related to comorbidities in comparison to immunocompromising conditions. The main limitation, on the other hand, is that the number of immunocompromised patients was relatively low, compared with the number of patients in the other two groups, which may have affected the statistical analyses. Secondly, the study comprised the early Wuhan variant-dominant period of COVID-19 and the findings may not be applicable to the current Omicron period.

CONCLUSION

In conclusion, this study has clearly shown that ICHs with COVID-19 have a higher risk of clinical worsening and of mortality. Besides, immunocompetent patients with comorbidities also have a higher risk of worse clinical course and mortality compared with the control patients, but their risk of death was lower than the ICH.

Conflict of interest: Authors declare no conflict of interest.

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