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Are High Urea Values before Intravenous Immunoglobulin Replacement a Risk Factor for COVID-19 Related Mortality?

İntravenöz İmmünoglobulin Replasmanı Öncesi Yüksek Üre Değerleri COVID-19'a Bağlı Mortalite için Bir Risk Faktörü müdür?

Emel ATAYİK
0000-0002-7011-7752
Gökhan AYTEKİN
0000-0002-9089-5914

Division of Allergy and Clinical Immunology, University of Health Sciences Konya City Hospital, Konya, Türkiye

ABSTRACT

Aim: This study aimed to examine the data of the coronavirus disease 2019 (COVID-19) patients treated with intravenous immunoglobulin (IVIG) treatment and to investigate the effects of the patients' clinical, laboratory, and treatment characteristics and risk factors for mortality.

Material and Methods: The study evaluated 81 adult COVID-19 patients who were hospitalized for the treatment of COVID-19 between April 2020 and September 2020 and were followed up, treated, and consulted in the immunology clinic for IVIG treatment, in a retrospective manner.

Results: The univariate analyses revealed that the duration of hospitalization in service, being intubated, duration of IVIG treatment, and the urea value before IVIG treatment were related to mortality in COVID-19 patients treated with IVIG treatment. As a result of multivariate analysis, being intubated and urea value before IVIG treatment were found to be independent risk factors for mortality (p=0.001 and p=0.009, respectively). It was found that for the 60 mg/dL level of urea value before IVIG treatment to predict mortality, the sensitivity was 46.2%, and the specificity was 35.5%. The area under the curve was found as 0.647; 95% confidence interval 0.518-0.776 (p=0.029).

Conclusion: The study found that urea values before IVIG treatment were a risk factor for mortality in patients who received IVIG treatment for COVID-19. This is important as it indicates that urea values should be closely monitored in patients given IVIG treatment for COVID-19. It also suggests that when resources are limited and risk stratification is required in COVID-19 patients, urea values can be helpful.

Keywords: SARS-CoV-2; immunoglobulin; mortality; blood urea nitrogen; COVID-19.

ÖZ

Amaç: Bu çalışmanın amacı, intravenöz immünoglobulin (IVIG) tedavisi ile tedavi edilen koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarının verilerini incelemek ve hastaların klinik, laboratuvar ve tedavi özellikleri ile mortalite için risk faktörlerinin etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmada, Nisan 2020 ile Eylül 2020 tarihleri arasında COVID-19 tedavisi için hastaneye yatırılan ve IVIG tedavisi için immünoloji kliniğinde takip, tedavi ve konsülte edilen 81 erişkin COVID-19 hastası geriye dönük olarak değerlendirilmiştir.

Bulgular: Tek değişkenli analizler, IVIG tedavisi ile tedavi edilen COVID-19 hastalarında hastanede yatış süresi, entübe olma, IVIG tedavi süresi ve IVIG tedavisi öncesi üre değerinin mortalite ile ilişkili olduğunu gösterdi. Çok değişkenli analiz sonucunda, entübe olma ve IVIG tedavisi öncesi üre değeri mortalite için bağımsız risk faktörleri olarak bulundu (sırasıyla, p=0,001 ve p=0,009). Mortaliteyi öngörmek için IVIG tedavisi öncesi 60 mg/dL üre değeri için duyarlılık %46,2 ve özgüllük ise %35,5 olduğu bulundu. Eğri altında kalan alan 0,647; %95 güven aralığı ise 0,518-0,776 olarak bulundu (p=0,029).

Sonuç: Çalışmada, COVID-19 nedeniyle IVIG tedavisi alan hastalarda IVIG tedavisi öncesi üre değerlerinin mortalite için bir risk faktörü olduğu bulundu. Bu, COVID-19 için IVIG tedavisi verilen hastalarda üre değerlerinin yakından izlenmesi gerektiğini göstermesi açısından önemlidir. Ayrıca, COVID-19 hastalarında kaynaklar sınırlı olduğunda ve risk sınıflandırması gerektiği durumlarda, üre değerlerinin yardımcı olabileceğini göstermektedir.

Anahtar kelimeler: SARS-CoV-2; immunoglobulin; mortalite; kan üre nitrojen; COVID-19.

Corresponding Author
Sorumlu Yazar
Emel ATAYİK
emelakinci@yahoo.com

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected the whole world in economic, social, spiritual, and many other areas, particularly in the field of health, since December 2019, when it was first described (1,2). As the disease is highly contagious, the virus spread worldwide in a short time and caused one of the most catastrophic pandemics in human history (3). Although there are some vaccines to reduce virus transmission and develop protection against it, it is obvious that vaccinating all the people in the world will not be possible in a short term. Although it has been more than one year since the World Health Organization (WHO) accepted COVID-19 as a pandemic, there is still no effective treatment. Until now, many treatment options, particularly antimalarial drugs and antivirals, systemic corticosteroids, tocilizumab, anakinra, conventional plasma therapy, and intravenous immunoglobulin (IVIG) therapy, have been tried in the form of monotherapy or combinations for treating COVID-19, there is still no consensus on its treatment (4-7). For this reason, it becomes crucial that the physicians interested in COVID-19 treatment share all the data they acquire, particularly in vulnerable patient groups, to reduce morbidity and mortality. Regarding COVID-19 treatment management, many countries have created their treatment protocols, and many associations have published guidelines for its treatment. COVID-19 treatment in Turkey has been primarily applied in line with the Ministry of Health protocols. In general, the patients positive for SARS-CoV-2 polymerase chain reaction (PCR) were put on hydroxychloroquine and favipiravir treatment at appropriate doses. Patients who did not benefit from these treatments and/or had underlying risk factors were hospitalized. In addition to respiratory support treatments, patients were treated with conventional plasma, systemic steroid therapy, immunomodulatory therapies such as tocilizumab and anakinra, and IVIG treatment, whichever appropriate, as line therapies (8). IVIG was administered as per the clinical immunologists' opinions and in the proper dose and time intervals.

Considering that pulmonary lesions in COVID-19 are caused by viral infiltrates and inflammatory response, IVIG treatment provides inflammatory cytokine balance, inhibits auto-reactive T cells, reduces antibody production from CD19+ B cells, and reduces macrophage activity. The IVIG treatment is thought to provide a regression in pulmonary lesions, reducing the need for mechanical ventilation, length of hospital stay, and mortality rates in these patients (9,10). Therefore, this study aimed to retrospectively examine the data of patients who reported to the immunology clinic for IVIG treatment in a tertiary referral hospital and who were hospitalized, followed up, and treated for COVID-19. The study also investigated the effects of the patients' clinical, laboratory, and treatment characteristics and risk factors for mortality in patients with COVID-19 treating with IVIG treatment.

MATERIAL AND METHODS

The study included adult COVID-19 patients who were hospitalized for the treatment of COVID-19 in a tertiary referral hospital (University of Health Science Konya Education and Research Hospital) between April 2020 and September 2020 and were followed-up, treated, and consulted in the immunology clinic for IVIG treatment in a retrospective manner. A review of medical records (including information on age, sex, and disease duration) was undertaken. Venous blood samples for biochemical analyses were drawn after at least ten hours of fasting, early in the morning. All biochemical analyses were conducted in the Central Biochemistry Laboratory of the Konya Education and Research Hospital. Laboratory measurements of the patients at the first admission to the hospital, at the time of hospitalization, and before IVIG treatment were used.

Complete blood counts were performed using Sysmex XN-10 (Sysmex Corporation, Kobe, Japan) analyzers with the fluorescent flow cytometry method. Serum creatinine levels were measured using the Jaffe method. Quantitative determination of serum IgG, IgM, IgA, and IgE was done through particle-enhanced immunonephelometry using the Siemens BN II/BN ProSpec system (Erlangen, Germany).

The follow-up period of all patients started with their hospitalization. For the patients who died, the number of days between the date of hospitalization and death was accepted as the follow-up period. The duration of follow-up was calculated by confirming whether the discharged patients were alive or not through the Republic of Turkey Death Reporting System, two weeks after discharge. For patients who died within two weeks of discharge, the follow-up period was accepted as the number of days between the date of hospitalization and death. For patients who lived more than two weeks after discharge, the follow-up period was calculated by adding 14 days to the number of days they stayed in the hospital.

IVIG treatment dose was calculated from a total dose of 2 gr/kg. The total dose was given to the patients in 3-5 days. Dose adjustment in obese patients was based on ideal body weight. In order not to cause renal burden, a 10% concentration of IVIG preparations that do not contain maltose and sucrose were preferred.

The time until hospitalization, resulting from the emergence of SARS-CoV-2-related symptoms such as fever, cough, and body pain, was considered the duration of illness. The duration of the follow-up in the service was specified as the day of hospitalization and the follow-up period in the intensive care unit (ICU) as the duration of intensive care hospitalization. All patients in the study received IVIG treatment. Some patients were followed only in the service and received IVIG treatment in the service. Some patients received IVIG treatment in the ICU. Patients who received IVIG treatment in the service and those who received IVIG treatment in the first 24/48 h after their admission to intensive care were specified as the IVIG treatment ICU first 24/48 h.

The systemic inflammatory index (SII) was calculated by the formula platelet x neutrophil/lymphocyte counts. The SARS-CoV-2 diagnosis was established with the detection of the SARS-CoV-2 genome via the PCR method from the nasopharyngeal sample (nasal swab) in patients with symptoms suggestive of SARS-CoV-2 infection such as fever, cough, shortness of breath, joint and body pain, and/or viral infiltration on lung imaging (PA chest radiography or lung tomography).

The permission for the study was obtained from the Republic of Turkey, Ministry of Health Scientific Research Platform. In addition, an ethics committee approval was obtained from Karatay University Ethics Committee (with the decision dated 09.02.2021, and numbered 2020/021). The study was conducted as per the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using the SPSS version 22.0 software package (IBM Corp., Armonk, NY, USA). The normality of the data was tested with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean±standard deviation, and data that were not normally distributed were expressed as median, interquartile range, and minimum-maximum. Descriptive data were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test. Comparisons between baseline characteristics were performed by independent samples t or Mann-Whitney U tests, where appropriate. Independent predictors for mortality were determined using Cox regression analysis with the backward: Wald model. Receiver operator characteristics (ROC) curve analysis was used to determine the most appropriate cut-off for the urea level. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 81 patients, 27 (33.3%) female and 54 (66.7%) male, were included in the study. The median age of the patients was 71 (range, 41-94) years. During the follow-up, the mortality rate was 64.2% (n=52). The rate of intubated patients was 45.7% (n=37). The median follow-up period was 19 (range, 1-60) days. The duration of hospitalization was 16 (range, 1-44) days, and the duration of hospitalization in intensive care was 10 (range, 0-31) days. All patients received hydroxychloroquine and favipiravir treatment during their follow-up. In addition, IVIG treatment was given to all patients. While 35 (43.2%) patients received tocilizumab treatment, 15 (18.5%) patients received conventional plasma and 33 (40.7%) patients received pulse steroid treatment. Fifty (61.7%) of the patients in the first 24 h of their admission to intensive care and 52 (64.2%) of the patients in the first 48 h of their admission to intensive care received IVIG treatment.

There was no statistically significant difference between the patients who died during their follow-up and the patients who survived in terms of age, gender, tocilizumab treatment, conventional plasma treatment, and the number of days of hospitalization in the service. We observed significant differences in terms of intubated patient ratio, pulse steroid therapy, white blood cell count on hospitalization, platelet count on hospitalization, lymphocyte percentage before IVIG treatment, C-reactive protein (CRP) values on hospitalization and before IVIG treatment, urea values before IVIG treatment, SII levels on hospitalization and before IVIG treatment, and neutrophil to lymphocyte ratio (NLR) levels before IVIG treatment. The demographic, laboratory and clinical characteristics of the patients have been summarized in Table 1, Table 2, Table 3, and Table 4.

Table 1. Baseline demographic and clinical parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
Gender, n (%)				
Male	35 (67.3)	19 (65.5)	0.870	54 (66.7)
Female	17 (32.7)	10 (34.5)		27 (33.3)
Age (years)	72.5 (59.5-77) [41-94]	70 (59-76) [46-78]	0.391	71 (60-76.5) [41-94]
Follow up time (day)	20 (12.25-28.75) [1-38]	16 (12-28) [3-60]	0.745	19 (12-28.5) [1-60]
Duration of illness (day)	7 (5-10) [3-10]	7 (5-8) [3-8]	0.846	7 (5-8.50) [3-10]
Duration of hospitalization (day)	17 (10-27) [1-38]	16 (12-28) [3-44]	0.557	16 (10.5-27) [1-44]
Duration of inpatient service (day)	7 (3-9) [0-31]	10 (3-14.5) [0-21]	0.055	7 (3-11) [0-31]
Duration of intensive care (day)	10 (5-19) [0-31]	13 (6.75-16.5) [2-21]	0.509	10 (5-17) [0-31]
Intensive care, n (%)	48 (92.3)	18 (62.1)	**0.001**	66 (81.5)
Intubation, n (%)	34 (65.2)	3 (10.3)	**0.001**	37 (45.7)
Comorbidity, n (%)	40 (76.9)	20 (69.0)	0.433	60 (74.1)

Descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 2. Treatment parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
Convalescent plasma, n (%)	9 (17.3)	6 (20.7)	0.707	15 (18.5)
Pulse steroid therapy, n (%)	28 (53.8)	5 (17.2)	**0.001**	33 (40.7)
Tocilizumab treatment, n (%)	19 (36.5)	16 (55.2)	0.105	35 (43.2)
IVIG treatment at least 3 days, n (%)	42 (80.8)	26 (89.7)	0.296	68 (84)
IVIG treatment in first 24 h, n (%)	30 (57.7)	20 (69.0)	0.317	50 (61.7)
IVIG treatment in first 48 h, n (%)	32 (61.5)	20 (69.0)	0.504	52 (64.2)
Duration of IVIG treatment (day)	3 (3-4) [1-5]	3 (3-5) [2-5]	0.069	3 (3-5) [1-5]
IVIG dose (gr/day)	40 (35-50) [25-50]	40 (35-50) [30-50]	0.832	40 (35-50) [25-50]

IVIG: intravenous immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 3. Laboratory parameters of the study group

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
WBC count ($\times 10^9$ /L)				
On hospitalization	8185 (5995-11170) [1176-27350]	5820 (4345-9040) [2630-20110]	**0.020**	7960 (5280-10460) [1176-27350]
Before IVIG treatment	11955 (7687-17342) [430-27290]	8190 (5435-10695) [1220-25920]	**0.008**	9570 (7430-15685) [430-27290]
Lymphocyte percentage ($\times 10^9$ /L)				
On hospitalization	9.95 (6.10-15.675) [2.20-30.00]	12.10 (7.70-24.45) [3.00-33.10]	0.081	10.90 (6.25-17.15) [2.20-33.10]
Before IVIG treatment	3.35 (2.375-6.00) [0.80-46.50]	5.60 (4.05-10.80) [2.60-35.70]	**0.001**	4.30 (2.90-4.30) [0.80-46.50]
Neutrophil percentage ($\times 10^9$ /L)				
On hospitalization	86.4 (77.8-90.8) [56.4-96.6]	75.0 (63.3-87.0) [26.1-94.2]	**0.001**	84.5 (74.0-89.5) [26.1-96.6]
Before IVIG treatment	93.2 (90.8-94.3) [70.9-97.4]	89.8 (81.0-92.8) [41.9-95.7]	**0.020**	92.0 (86.0-94.1) [41.9-97.4]
Platelet count ($\times 10^3$)				
On hospitalization	205 (165.5-269.5) [71-372]	166 (131.5-214.5) [75-422]	**0.030**	186 (147-258) [71-442]
Before IVIG treatment	242 (158.0-346.2) [75-512]	231 (170.5-299.5) [27-401]	0.395	232 (162-313) [27-512]
Fasting blood glucose (mg/dL)				
On hospitalization	154 (117.75-215.75) [84-361]	122 (97.5-167) [75-480]	**0.034**	140 (103-191) [75-480]
Before IVIG treatment	172 (118.50-215.50) [88-344]	141 (119-229) [77-263]	0.195	157 (115-215) [77-344]
Urea (mg/dL)				
On hospitalization	42.5 (32-62) [15-256]	41 (29-70.5) [17-180]	0.863	42 (30.5-66.5) [15-256]
Before IVIG treatment	57.5 (46-92) [33-230]	44 (36.5-72) [17-79.1]	**0.029**	55 (42.5-77.5) [17-230]
Creatine (mg/dL)				
On hospitalization	1.04 (0.90-1.26) [0.58-6.87]	1.02 (0.85-1.24) [0.60-2.20]	0.629	1.03 (0.90-1.91) [0.58-6.87]
Before IVIG treatment	0.89 (0.75-1.13) [0.52-2.60]	0.87 (0.71-1.02) [0.50-1.22]	0.544	0.89 (0.75-1.05) [0.50-2.60]
IgG (mg/dL), on hospitalization	10.60 (6.72-11.50) [5.9-13.8]	7.69 (3.29-10.02) [0.0-16.1]	0.136	8.59 (5.75-10.85) [0.0-16.1]
IgM (mg/dL), on hospitalization	0.42 (0.36-0.67) [0.20-1.88]	0.60 (0.38-0.85) [0.17-1.21]	0.573	0.44 (0.39-0.73) [0.17-1.88]
IgA (mg/dL), on hospitalization	2.52 (2.15-3.53) [0.37-7.62]	2.45 (1.25-2.89) [0.24-3.32]	0.198	2.50 (1.86-2.94) [0.24-7.62]

IVIG: intravenous immunoglobulin, WBC: white blood cell, Ig: immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

Table 4. Inflammatory parameters of the patients

Variable	Non-survivor (n=52)	Survivor (n=29)	p	Total (n=81)
CRP (mg/L)				
On hospitalization	124 (47-159) [3-415]	66 (35.9-102.0) [8.5-317]	**0.015**	91.2 (41.5-146.8) [3.0-415]
Before IVIG treatment	82 (13-128) [3.1-297]	21 (6.1-65.1) [3.1-197]	**0.012**	47.0 (8.6-120.5) [3.1-297]
SII				
On hospitalization	1953.0 (1024.6-3393.4) [254.2-11059.8]	823.1 (432.3-2684.9) [352.9-12962.4]	**0.016**	1558.8 (670.4-3128.3) [254.2-12962.4]
Before IVIG treatment	6676.9 (2890.1-10383.1) [657.7-22356.5]	3567.0 (1494.1-546.1) [1354.7-13441.4]	**0.013**	4897.3 (2119.3-8419.5) [657.7-22356.5]
NLR				
On hospitalization	9.06 (5.30-14.73) [1.93-42.21]	6.12 (2.94-11.83) [1.86-30.72]	0.075	8.26 (4.45-14.38) [1.86-42.21]
Before IVIG treatment	27.81 (14.44-38.01) [2.33-126.31]	16.15 (7.64-23.27) [5.80-27.66]	**0.001**	19.39 (11.12-32.73) [2.33-126.31]

CRP: C-reactive protein, SII: systemic inflammatory index, NLR: neutrophil to lymphocyte ratio, IVIG: intravenous immunoglobulin, descriptive statistics were reported as median (1st quartile - 3rd quartile) [minimum - maximum] for numerical variables

The univariate analyses revealed that the duration of hospitalization in service, being intubated, duration of IVIG treatment, and the urea value before IVIG treatment were related to mortality in patients treated with IVIG treatment (p=0.043, p=0.001, p=0.074, and p=0.004, respectively). As a result of multivariate analysis, being intubated and urea value before IVIG treatment were found to be independent risk factors for mortality (p=0.001 and p=0.009, respectively, Table 5).

It was found that for the 60 mg/dL level of urea value before IVIG treatment to predict mortality in COVID-19 patients receiving IVIG treatment, the sensitivity value was 46.2%, and the specificity was 35.5%. The area under the curve (AUC) was found 0.647 with a 95% confidence interval (CI) of 0.518-0.776 (p=0.029, Figure 1).

Table 5. Independent risk factors for mortality

Variable	HR (95% CI)	p
Intubation	0.389 (0.218 - 0.693)	**0.001**
Urea, before IVIG treatment	1.009 (1.002 - 1.017)	**0.009**

IVIG: intravenous immunoglobulin, HR: hazard ratio, CI: confidence interval

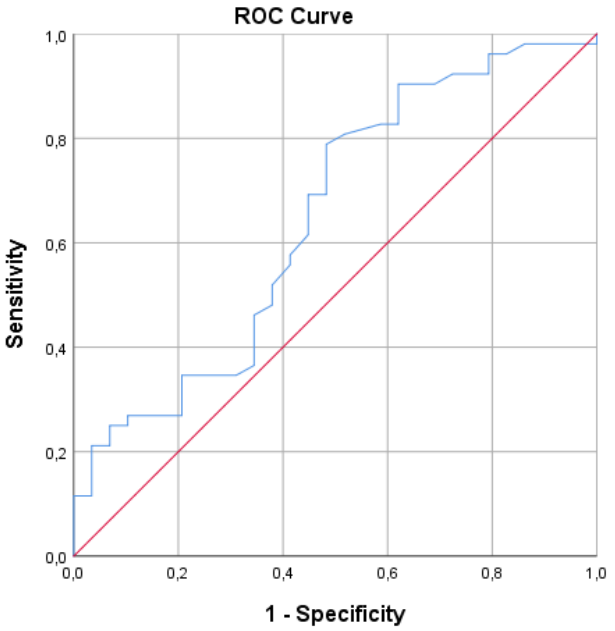

Figure 1. ROC curve of urea level before IVIG treatment

DISCUSSION

The SARS-CoV-2 virus has caused one of the most severe pandemics in human history and has put a lot of pressure, particularly on healthcare systems, since March 2020, when it was declared as a pandemic by WHO. The virus has caused the deaths of approximately 3 million people in nearly one year since its outbreak (2,11). At present, there is no globally accepted treatment scheme for treating patients hospitalized for COVID-19. Therefore, it is crucial to determine the prognostic factors in vulnerable patient groups and to develop treatment modalities specific to patient groups according to these factors to reduce mortality and morbidity. In line with this opinion, this study found that being intubated and urea values before IVIG treatment are independent risk factors for COVID-19-related mortality in patients hospitalized for COVID-19 and given IVIG treatment.

Acute renal failure development has been reported in 7% of COVID-19 patients (12,13). In addition, renal failure has been reported to increase COVID-19-related hospital deaths in mortality studies (14-19). Cheng et al. (15) showed an increase in blood urea nitrogen (BUN) that increased mortality 3.97 times in COVID-19 patients. Another study reported that the hospitalization BUN and D-dimer levels were associated with mortality, and BUN values of ≥4.6 mmol/L included a high risk for hospital deaths (14). In another study, 6.29% of COVID-19 patients showed an increase in BUN, and increased basal BUN and creatinine values were reported to cause high mortality (17). Ng et al. (18) reported that being intubated and BUN values are risks for hospital mortality in patients with end-stage renal disease and COVID-19. Although the increase in BUN after SARS-CoV-2 is frequent, the reason for this increase is not clear. Renal epithelial cells contain angiotensin-converting enzyme 2 (ACE2) receptors that are 100 times more intense than respiratory epithelial cells; SARS-CoV-2 is internalized to renal cells and may cause renal function loss with a cytopathic effect (15,20). It has been suggested that this may increase the absorption of BUN from the renal tubules by activating the renin-angiotensin-aldosterone system (20). Although IVIG treatment is often used as one of the last treatment options in patients who do not respond to other treatments, IVIG treatment itself may be associated with renal damage (13). On the other hand, the increase in BUN levels in COVID-19 patients may be an indicator of kidney dysfunction and an increased inflammatory state. The renal load caused by increased catabolism, hypovolemia-induced renal hypoperfusion, sepsis, drugs used in the treatment of COVID-19 such as steroid therapy, and rhabdomyolysis may also cause an increase in BUN. Although creatinine, another indicator of renal damage, was not found to be a predictor of mortality in this study, the fact that BUN is predictive of mortality suggests that BUN increases due to inflammatory conditions rather than a renal-induced reason and that increased inflammatory processes play a role in making BUN a risk factor for mortality. Another situation supporting this hypothesis is that inflammatory markers of the patients who died before IVIG treatment were prominently higher and statistically significant than those of alive patients. As the most common cause of mortality in COVID-19 is a respiratory failure caused by cytokine storm, the majority of patients (81.5%) in the present study had to be followed up in the ICU due to deterioration in their clinical condition. IVIG treatment is one of the last options in COVID-19 patients who are unresponsive to other therapies and whose cytokine storms are not controlled. It was thought that these patients face an intense inflammatory process, which causes an increase in BUN.

The retrospective design, relatively small size of study group, lack of evaluation of other renal markers such as proteinuria and hematuria, and lack of knowledge of what happened in the post-follow-up period form the main limitations of this study.

CONCLUSION

The study found that urea values before IVIG treatment were a risk factor for mortality in patients who received IVIG treatment for COVID-19. This is important as it indicates that BUN values should be closely monitored in patients given IVIG treatment for COVID-19. It also suggests that when resources are limited and risk stratification is required in COVID-19 patients, BUN values can be helpful.

Ethics Committee Approval: The study was approved by the Ethics Committee of KTO Karatay University Faculty of Medicine (09.02.2021, 21).

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