Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Factors affecting mortality in COVID-19 patients treated with intravenous immunoglobulin

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ARTICLE INFO

Keywords:
COVID-19
Intravenous immunoglobulin
Charlson Comorbidity Index
Immunoglobulin A
Mortality

Received: Jun 20, 2023
Accepted: Aug 18, 2023
Available Online: 25.08.2023

DOI:
10.5455/annalsmedres.2023.06.140

Abstract

Aim: Intravenous immunoglobulin (IVIG), used as an option in the treatment of severe Coronavirus disease 2019 (COVID-19), has been shown to have effects on the suppression of the hyperinflammatory state through immunomodulatory actions. The aim of our study was to evaluate the factors associated with mortality in patients treated with IVIG for COVID-19.

Materials and Methods: Patients diagnosed with COVID-19 and receiving IVIG therapy in addition to standard care therapy were included in the study.

Results: A total of 46 patients who received IVIG treatment were included in the study. The mortality rate was higher in patients aged over 52 years (p:<0.001). The mortality rate was found to be higher in patients with an interval of more than 7 days between hospitalization and the start of IVIG treatment (p:0.009). Patients with a higher Charlson Comorbidity Index (CCI) score had a more mortal course (p<0.001). Mortality rate was higher in patients with high immunoglobulin A (Ig A) levels before IVIG treatment (p:0.004). Survival rate was lower in patients with high neutrophil lymphocyte ratio (NLR), urea and prothrombin time (PT)and low albumin and lymphocyte counts.

Conclusion: A high Charlson Comorbidity Index score and high immunoglobulin A level are poor prognostic in COVID 19 patients treated with IVIG. Studying mortality risk factors is valuable in predicting response to IVIG therapy and may help in early identification of patients with poor prognosis and re-evaluate of treatment strategy.

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization in March 2020, causing hundreds of thousands of patient deaths with millions of confirmed cases [1]. COVID-19 can cause mild symptomatic infection as well as fatal immunological complications such as severe life-threatening pneumonia and cytokine storm [2]. One of the factors causing severe disease in COVID-19 is the overexpression of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α) and interferon [3]. The aggressive inflammatory response caused by COVID-19 has been shown to be associated with lung injury and multiple organ failure [4]. In addition to standard treatments in severe COVID-19 cases, it has been recommended to use anticytokine and immunomodulatory therapies against hyperinflammation and the cytokine storm that occurs [5,6]. Rapid recognition and suppression of hyperinflammation in severe cases has been shown to reduce the risk of mortality and morbidity [2]. IVIG is a plasma product containing polyclonal immunoglobulin gamma obtained from healthy donors. It has been previously used in diseases caused by severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses and favorable effects have been observed. IVIG has been shown to have effects on the suppression of the hyperinflammatory state through immunomodulatory actions such as binding to cytokines and variable sites of other antibodies [7]. Many studies have been conducted on factors affecting mortality in COVID-19 patients [8,9,10]. There are studies showing that IVIG treatment reduces the mortality rate in severe

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COVID-19 disease, as well as studies reporting that IVIG does not affect mortality [11,12]. We could not find a study explaining the reason for this variability in our literature review.

The aim of our study was to evaluate the factors associated with mortality in patients treated with IVIG for COVID-19.

Materials and Methods

The electronic file data of the patients who were hospitalized in the covid service and intensive care unit (ICU) of Recep Tayyip Erdogan University Faculty of Medicine between March 20, 2020, and March 20, 2022, and diagnosed with COVID-19 pneumonia by reverse transcription-polymerase chain reaction (RT-PCR) and thorax computed tomography (thorax CT) method, were retrospectively analyzed. Patients older than 18 years of age and receiving IVIG treatment in addition to the standard care treatment specified in the COVID-19 adult patient treatment guideline of the Ministry of Health due to COVID-19 pneumonia were included in the study. Pre-sample size analysis was not performed because the study was retrospective and all patients who met the inclusion criteria on the specified dates were included in the study. Patients were divided into two groups as survivors and deceased. Age, gender and comorbidity status of the patients were determined. Immediately before the IVIG treatment, the levels of white blood cell, neutrophil, lymphocyte, neutrophil to lymphocyte ratio (NLR), hemoglobin, platelet, glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, total protein, albumin, lactate dehydrogenase, total bilirubin, direct bilirubin, sodium, potassium, calcium, magnesium, C-reactive protein, procalcitonin, ferritin, prothrombin time (PT), activated partial thromboplastin time, fibrinogen, D-dimer, immunoglobulin G, immunoglobulin A, immunoglobulin M and blood gas; pH, SaO_2, pCO_2, PaO_2, HCO_3, lactate the patients were determined and were recorded.

Patients who received the commercial drug Intratect (plasma-derived normal human immunoglobulin) of Biotest AG (Germany) at a dose of 1 g/kg intravenously for 2 days during clinical hospitalization were determined. The time between hospitalization and IVIG treatment and the length of hospital stay were calculated. Patients who needed high flow oxygen, received anticytokine therapy,received bilevel positive airway pressure (BIPAP) and were intubated during clinical follow-up were determined. Charlson Comorbidity Index (CCI) score was calculated in terms of association with mortality.

Our study's ethics committee approval was obtained from Recep Tayyip Erdogan University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee chairmanship. The study was conducted according to the Declaration of Helsinki. Ethical approval no: 2022/135.

Statistical analysis

Statistical analyses were performed by using the SPSS program (IBM, SPSS Inc., Version 23.0, Chicago, USA). Shapiro-Wilk analysis of normality was used to evaluate the distribution of the numerical data. Categorical variables were expressed as frequency and percentage (%), and numerical variables were expressed as mean ± standard deviation or median (min. to max.) where appropriate. The relationship between categorical variables with survival was evaluated with the Chi-Square test (Pearson chi-square and Fisher's Exact Test) considering the size of the patient groups in the categories. In group comparisons, Student's T-Test or Mann-Whitney U test were used to compare continuous numerical variables. Receiver operating characteristic (ROC) analysis was performed to determine the laboratory findings' cut-off values, as well as their sensitivity and specificity. Kaplan-Meier method and Log-rank test were carried out to analyze the correlation between variables and survival. A p-value of <0.05 was considered for statistical significance.

Results

A total of 46 patients who were hospitalized due to COVID-19 and treated with IVIG were included in this study. The mean age of the surviving group (n:18) was 45.9 years, while the mean age of the deceased patients (n:28) was 62 years. The mortality rate was higher in the patient group aged over 52 years (p:$<$0.001). No significant difference was found between the surviving and deceased patient groups in terms of gender (p: 0.639). The mortality rate was higher in patients with a duration of more than

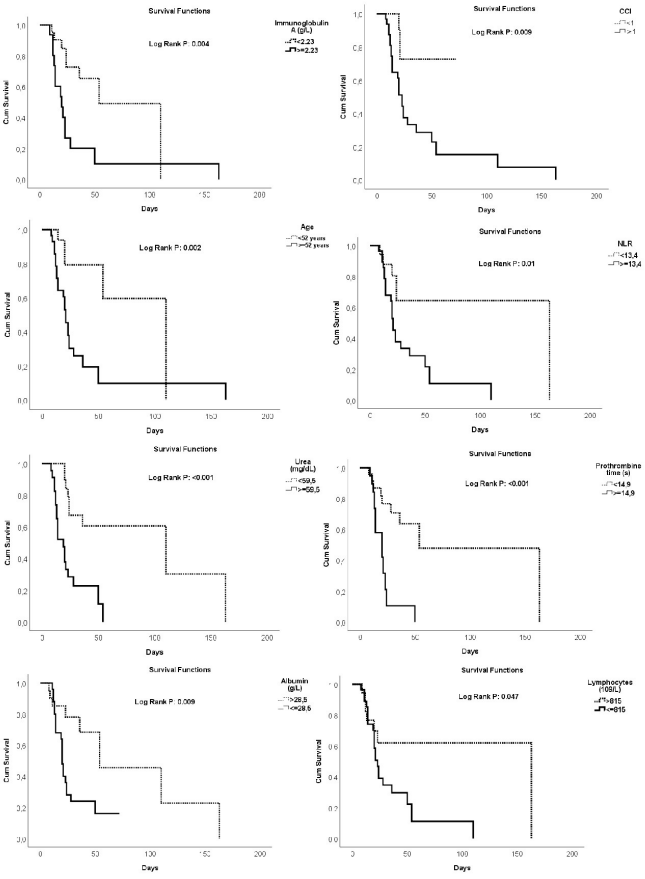

Figure 1. Kaplan Meier survival curve for Immunoglobulin A (Ig A), Charlson Comorbidity Index (CCI), Age, Neutrophil to lymphocyte ratio (NLR), Urea, Prothrombine time (PT), Albumin and Lymphocyte.

Table 1. Demographic data and laboratory parameters of the patients.

	Survival		
	Survivor	Exitus	
	Mean ± SD	Mean ± SD	p
	Median (min - max)	Median (min - max)	
Age	45.9 ± 13.7	62 ± 13.2	**<0.01**
Hospitalization Duration	32 (8 - 72)	20 (8 - 163)	0.055
Charlson Comorbidity Index	0 (0 - 2)	2 (0 - 5)	**<0.01**
White blood cells (109/L)	12.216.1 ± 4312.6	13.960 ± 6.286.7	0.309
Neutrophils (109/L)	10.921.1 ± 4.032.2	12.877.9 ± 6.214.8	0.243
Lymphocytes (109/L)	853.9 ± 351.8	610 ± 301.5	**0.016**
Neutrophil to lymphocyte ratio	11.8 (6.2 - 30.2)	17.2 (1.9 - 147.5)	**0.022**
Monocytes (109/L)	356.1 ± 180.2	444.3 ± 301.6	0.27
Hemoglobin (g/L)	12.7 ± 2	12.2 ± 1.9	0.398
MCV (fL)	89.8 ± 6.2	90 ± 6.9	0.899
Platelets (109/L)	262.7 ± 106.9	231.1 ± 92.3	0.293
RDW	43.8 ± 4.5	45.6 ± 6.1	0.293
MPV (fL)	9.9 ± 1.3	10.2 ± 1	0.328
PDW	16.5 ± 0.5	16.4 ± 0.3	0.7
Glucose (mg/dL)	149.3 ± 48.3	183.4 ± 70.1	0.079
Urea (mg/dL)	48 (24 - 92)	76 (38 - 213)	**0.002**
Creatinine (mg/dL)	0.7 (0.3 - 3.9)	0.8 (0.4 - 3.7)	0.213
AST (U/L)	52.5 (19 - 268)	40.5 (17 - 57)	0.176
ALT (U/L)	79.5 (15 - 235)	33 (12 - 170)	**0.003**
Total protein (g/L)	60 ± 7	54 ± 7	**0.005**
Albumin (g/L)	31 ± 4	27 ± 3	**0.001**
GGT (U/L)	101.5 (28 - 339)	50.5 (14 - 423)	**0.032**
LDH (U/L)	617.2 ± 271.3	630.5 ± 242.4	0.863
Total bilirubin (mg/dL)	0.6 (0.3 - 1.4)	0.6 (0.2 - 2)	0.429
Direct bilirubin (mg/dL)	0.1 (0.1 - 0.2)	0.2 (0 - 0.8)	0.081
Sodium (mmol/L)	137.9 ± 4.1	141.5 ± 7	0.06
Potassium (mmol/L)	4 ± 0.4	4.2 ± 0.5	0.062
Calcium (mg/dL)	8.6 ± 0.5	8.1 ± 0.9	**0.015**
Magnessium (mg/dL)	2.2 ± 0.3	2.1 ± 0.3	0.245
C reactive protein (mg/L)	41.1 (1 - 180)	48 (2.1 - 227)	0.14
Procalcitonin (ng/mL)	0.1 (0.1 - 1.4)	0.3 (0.1 - 8)	0.121
Ferritin (ng/mL)	997 (128 - 4720)	950 (167 - 5546)	0.578
Prothrombine time (s)	13.7 ± 1	16.5 ± 2.8	**<0.01**
Activated partial thromboplastin time (s)	26.1 (20.8 - 41.2)	28.4 (22.9 - 77)	0.183
Fibrinogen	397.4 ± 169.4	409.8 ± 156.4	0.81
D-dimer (mg/L)	2.9 (0.2 - 7.2)	2.5 (0.6 - 12.9)	0.478
Immunoglobulin G (g/L)	10 ± 3	9 ± 2.7	0.381
Immunoglobulin A (g/L)	1.7 ± 0.5	2.7 ± 1.4	**0.004**
Immunoglobulin M (g/L)	1.29 ± 0.9	1.12 ± 0.4	0.583
pH	7.4 ± 0.1	7.4 ± 0.1	0.111
SaO_2	91.5 ± 3.7	89.6 ± 5.5	0.258
paO_2	66.6 ± 10.2 6	4.6 ± 11.3	0.586
pCO_2	45.5 ± 12	49.5 ± 16.2	0.439
HCO_3	28.5 ± 3.7	26.8 ± 4.6	0.238
Lactate	1.9 ± 0.6	2.2 ± 0.8	0.276

MCV:Mean corpuscular volume, RDW:Red cell distribution width, MPV:Mean platelet volume, PDW:Platelet distribution width, AST:Aspartate amino transferase, ALT:Alanine aminotransferase, GGT:Gamma-glutamyl transferase, LDH:Lactate dehydrogenase, SaO_2: Oxygen saturation, PaO_2:Partial pressure of oxygen, PCO_2:Partial pressure of carbon dioxide, HCO_3:Bicarbonate.

Table 2. Therapy status of the patients.

		Survival		
		Survivor	Exitus	p
		n (%)	n (%)	
Gender	Female	7 (38.9)	9 (32.1)	0.639
	Male	11 (61.1)	19 (67.9)	
Intubation	Intubated	5 (27.8)	28 (100)	**<0.001**
	Non-intubated	13 (72.2)	0 (0)	
Pre-IVIG time	≤7 Days	9 (50)	4 (14.3)	**0.009**
	>7 Days	9 (50)	24 (85.7)	
BIPAP	BIPAP +	8 (44.4)	18 (64.3)	0.185
	BIPAP -	10 (55.6)	10 (35.7)	
High Flow	High Flow +	14 (77.8)	25 (89.3)	0.407
	High Flow -	4 (22.2)	3 (10.7)	
AnticytokineTreatment	Anticytokine -	3 (16.7)	9 (32.1)	0.315
	Anticytokine +	15 (83.3)	19 (67.9)	
Pre-IVIG Pulmonary Infiltration	CORADS 3	3 (16.7)	1 (3.6)	0.284
	CORADS 4	15 (83.3)	27 (96.4)	
Antiagregan/Anticoagulant Treatment	Enoxaparin	6 (33.3)	12 (42.9)	0.518
	ASA+Enoxaparin	12 (66.7)	16 (57.1)	

IVIG:Intravenous immunoglobulin, BIPAP:Bilevel positive airway pressure, ASA: Acetyl salicylic acid, HFNC:High-flow nasal cannula.

7 days between hospitalization and the initiation of IVIG treatment (p:0.009). Mortality was higher in the intubated patient group (p<0.001). While the median CCI score was 0 in the surviving patients, the median CCI score was 2 in the deceased patient group. Patients with a higher Charlson Comorbidity Index (CCI) score had a more mortal course (p<0.001). The mean Ig A level was 2.7 g/L in the deceased patient group and 1.7 g/L in the survivors. The mortality rate was higher in patients with high IgA levels before IVIG treatment (p:0.004). Demographic characteristics, biochemical parameters, hemogram, blood gas values and treatment status of the patients are given in Tables 1 and 2.

In ROC analysis, for in hospital survival evaluation IgA was found to have 63.6% sensitivity and 87.5% specificity at a cut-off value of 2.23 g/L (AUC:0.743; p=0.011). NLR was found to have 78.6% sensitivity and 61.1% specificity at a cut-off value of 13.4 (AUC: 0.702; p=0.022). Urea was found to have 67.9% sensitivity and 77.8% specificity at a cut-off value of 59,5 mg/dL (AUC: 0.774; p=0.002). PT was found to have 66.7% sensitivity and 93.7% specificity at a cut-off value of 14,9 mg/dL (AUC:0.856; p=<0.001). Albumin was found to have 71.4% sensitivity and 72.2% specificity at a cut-off value of 28,5 g/L (AUC:767; p=0.002). Lymphocyte count was found to have 75% sensitivity and 61.1% specificity at a cut-off value of 815(109/L) (AUC: 0.708; p=0.018). CCI was found to have 89.3% sensitivity and 61.1% specificity at a cut-off value of 1 (AUC: 0.812; p=<0.001). Age was found to have 82.1% sensitivity and 72.2% specificity at a cut-off value of 52 years (AUC:0.815; p=<0.001) (Figure 1).

Discussion

Our results revealed some parameters that positively and negatively affect mortality in COVID-19 patients receiving IVIG therapy.

In advanced age, deterioration in the immune system, defects in T lymphocyte and Blymphocyte function and overproduction of type 2 cytokines lead to prolonged proinflammatory responses and impaired control of viral replication. Studies have shown that advanced age (> 65 years) is an important risk factor for mortality in patients with severe COVID-19 [10]. In our study, the mean age was found to be higher in the deceased patient group compared to the survivors and IVIG treatment did not have a favorable effect on mortality in elderly patients.

There are studies reporting that the mortality rate in critically ill COVID-19 patients ranges between 15% and 74%, especially when invasive mechanical ventilation (IMV) is required [13,14,15]. There are many reasons for these high variable rates such as intubation time, disease severity, comorbid diseases, degree of lung damage, secondary infections, and strategies for the use of mechanical ventilation. In our study, only 5 of 33 intubated patients out of a total of 46 patients receiving IVIG treatment survived, while all non-intubated patients survived. This shows that IVIG treatment does not affect mortality in intubated patients with COVID-19 disease. In addition, giving IVIG treatment before patients reach the intubation limit may significantly increase survival. There may be a strong relationship between the efficacy of IVIG and the severity of COVID-19 disease.

In a study by Xie et al., IVIG treatment given within the first 48 hours in COVID-19 patients was shown to reduce ventilator use, shorten the duration of hospital and ICU stay, and ultimately reduce 28-day mortality [16]. It has been reported that viral replication reaches the highest level in the first 1 week after patients are infected with the virus and antiviral antibodies develop from the 2nd week. A study has shown that IVIG treatment applied in the early period can improve the prognosis of the disease [17]. Similarly, in our study, despite the side effects and high cost of IVIG, we found that administration of IVIG within the first 7 days after hospital admission accelerated the clinical recovery process and reduced disease-related mortality. This showed us the necessity of starting IVIG treatment in the early period before inflammation progresses.

In a study, it was found that serum Ig A levels were high in severe COVID-19 cases regardless of age, gender and comorbidities, and high titers were correlated with severe ARDS. It was thought that this may be due to the high viral antigen load to which the patients were exposed [18]. In our study, serum Ig A levels was found to be higher in the deceased patient group and was consistent with the literature. The high serum IgA level measured before IVIG treatment is valuable in predicting that the response to IVIG treatment will be inadequate in COVID-19 patients.

CCI is an easy-to-apply method used to predict the risk of death due to comorbid diseases and to evaluate survival and prognosis. According to the severity of morbidity, a score from one to six is given [19]. In a meta-analysis, it was shown that high CCI score was associated with increased mortality and disease severity in COVID-19 patients [20].In our study; it was observed that mortality was higher in COVID-19 patients with a CCI score above 1 and IVIG treatment did not affect mortality. Therefore, IVIG treatment may be more beneficial in patients with low CCI.

Lymphocytes have a critical role in the destruction of virus-infected cells. Inadequate regeneration of lymphocytes infected by the virus and especially a decrease in the number of CD4 T lymphocytes helps to predict the severe and mortal course of the disease. In case of inflammation, neutrophils and macrophages interact with many cell populations by increasing cytokine release. By releasing reactive oxygen radicals, they induce cellular DNA damage and allow the virus to exit the cell. Thus, it helps to kill the virus with antibody-mediated cytotoxicity. Studies have found that high NLR levels and lymphopenia are biomarkers associated with poor prognosis in COVID-19 patients [21,22]. In our study, similar to the literature, lymphopenia and elevated NLR were found in the deceased patient group and IVIG treatment was not effective enough in these patients.

Urea is the end product of protein metabolism and may increase due to many reasons such as ischaemia, hypovolemia and drug use and is a marker used to evaluate renal function. High urea level, which is also included in the curb 65 scoring system used to evaluate the severity of pneumonia, has been shown to be associated with mortality in covid 19 patients [23]. Albumine is a negative acute phase reactant. Inflammation increases capillary permeability, causing albumin to diffuse into the interstitial space and decreasing serum albumin level. Studies have shown that low albumin level is an independent risk factor for mortality in COVID-19 patients [24,25]. In our study, elevated urea and low albumin levels were found in deceased patients and it was observed that this group did not benefit from IVIG treatment.

Prothrombin time is a coagulation test used to evaluate various thromboembolic events and haemorrhagic disorders. In a study conducted in patients hospitalized due to COVID-19 pneumonia, it was shown that prolonged PT time was associated with poor prognosis [26,27]. In our study, it was found that IVIG treatment did not positively affect the course of the disease in patients with PT prolongation.

The limitations of our study are the small number of patients, the fact that it was performed in a single centre and the absence of a control group.

Conclusion

A high Charlson Comorbidity Index score and high immunoglobulin A level are poor prognostic in COVID-19 patients treated with IVIG. Studying mortality risk factors is valuable in predicting response to IVIG therapy and may help in early identification of patients with poor prognosis and re-evaluate of treatment strategy.

Ethical approval

Our study's ethics committee approval was obtained from Recep Tayyip Erdogan University Faculty of Medicine,

Non-Interventional Clinical Research Ethics Committee chairmanship (Ethical approval no: 2022/135).

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