Original Research

Efficacy of Intravenous Immunoglobulin Therapy for Patients With Sepsis and Low Immunoglobulin G Levels: A Single-Center Retrospective Study

Masayuki Akatsuka, MD, PhD[1]; Yoshiki Masuda, MD, PhD[1]; Hiroomi Tatsumi, MD, PhD[1]; and Tomoko Sonoda, DDS, PhD[2]

[1]Department of Intensive Care Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan; and [2]Department of Public Health, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan

ABSTRACT

Purpose: The efficacy of intravenous immunoglobulin (IVIG) administration in patients with sepsis or septic shock remains unclear. A single-center retrospective study was conducted to evaluate the association between IVIG supplementation and favorable outcomes in patients with sepsis and low serum immunoglobulin G (IgG) levels.

Methods: A total of 239 patients with sepsis were identified whose serum IgG levels were determined upon admission to the intensive care unit between January 2014 and March 2021. Patients with low IgG levels (<670 mg/dL) were divided into the IVIG and non-IVIG groups. Patient data were collected from electronic medical records to evaluate the patients' characteristics, sepsis severity, and prognosis. The primary outcome was 28-day mortality. The propensity score was calculated by using the following variables: age, Sequential Organ Failure Assessment score, immunocompromised status, and serum IgG levels. Logistic regression analysis using propensity score as the adjusted variable was performed to evaluate the outcome.

Findings: Of 239 patients, 87 had low IgG levels. Of these patients, 47 received IVIG therapy. The 28-day (odds ratio [OR], 0.15; 95% CI, 0.04–0.54; $P = 0.004$) and 90-day (OR, 0.31; 95% CI, 0.11–0.83; $P = 0.020$) mortality rates were significantly lower in the IVIG group than in the non-IVIG group. Moreover, the number of days free from renal replacement therapy was significantly higher in the IVIG group than in the non-IVIG group (OR, 1.06; 95% CI, 1.01–1.11; $P = 0.025$). Serum IgG levels in the IVIG group showed no significant difference compared with those in the non-IVIG group. No significant differences in the patients' characteristics were observed between the groups.

Implications: This study found that IVIG administration in patients with sepsis and low serum IgG levels was associated with improved prognosis. Further studies are warranted to evaluate the validity of IVIG therapy for patients with sepsis and low serum IgG levels. (*Clin Ther.* 2022;44:295–303.)

Key words: intensive care unit, intravenous immunoglobulin therapy, low immunoglobulin G level, outcome, retrospective study, sepsis.

INTRODUCTION

Sepsis is a complex disorder that develops from a dysregulated host response to infection, leading to the dysfunction of multiple organs and an increased risk of death in the intensive care unit (ICU).[1] Standardizations and advances in the management of patients with sepsis have reduced sepsis-related mortality over the last several decades.[2] A promising strategy in the treatment of sepsis is intravenous immunoglobulin

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(IVIG) therapy, which strengthens the host immune response by increasing bactericidal activity, stimulating leukocytes, and neutralizing bacterial endotoxins and exotoxins.[3] However, the results of clinical studies on the effects of IVIG therapy in patients with sepsis have been controversial; although some studies have reported that the use of IVIG improves patient survival rates,[4,5] others have shown that IVIG administration does not reduce sepsis-related mortality.[6–8] A recent meta-analysis found a significant reduction in mortality among patients with sepsis treated with IVIG[4]; in contrast, results from another meta-analysis that was performed using a randomized controlled trial (RCT) with a low risk for bias indicated no significant benefit.[9]

In sepsis, serum immunoglobulin G (IgG) levels are often low because of the consumption of IgG by activated innate immune cells, suppression of IgG production, and vascular leakage of immunoglobulins.[10] Studies have shown that decreased serum IgG levels are positively associated with the severity of critical illness and mortality in patients with sepsis.[11,12] Therefore, immunoglobulin supplementation is proposed to be an appropriate treatment for patients with sepsis and low IgG levels. However, to our knowledge, no studies have investigated the efficacy of IVIG therapy in sepsis patients presenting with low IgG levels. Thus, it remains unclear whether IVIG therapy improves the prognosis of these patients. We hypothesized that IVIG therapy would improve the prognosis of patients with sepsis and low IgG levels. To test this hypothesis, we investigated the efficacy of IVIG therapy in patients with sepsis who presented with low IgG levels by determining the association between IVIG supplementation and outcomes.

PARTICIPANTS AND METHODS

Study Design and Ethics Approval

This was a single-center, retrospective, observational study. The requirement for informed consent from patients was waived due to the retrospective nature of the study and the use of anonymized data. The study protocol was approved by the Institutional Review Board of Sapporo Medical University (authorization number 332-29).

Patients

Given that our ICU provides both medical and surgical services, patients admitted to the ICU from general wards and operating rooms were included in this study; patients from the emergency department were not. All patients admitted to the ICU between January 2014 and March 2021 were eligible for inclusion. Serum IgG levels were determined in patients with suspected infection at the discretion of the physician in charge immediately upon admission to the ICU (lower–upper limit, 815–1100 mg/dL). Sepsis and septic shock were defined according to the Sepsis-3 criteria.[13] The exclusion criteria were as follows: admission after elective surgery, age <15 years, death, or discharge from the ICU within 24 hours of admission. Patients with sepsis and septic shock with serum IgG levels <670 mg/dL were enrolled in this study because these patients had the potential for increased mortality, as previously reported.[12]

Patients were divided into 2 groups: (1) the IVIG group comprised patients who were administered polyclonal IVIG containing IgG; and (2) the non-IVIG group comprised patients who were not administered IVIG. For the IVIG group, inclusion criterion was receipt of IVIG therapy within 72 hours after ICU admission. The decision to administer IVIG was determined during discussions at ICU meetings regarding decision-making for individuals' treatment that are held twice a day and include the attending physician and the intensivists. All patients with sepsis were managed according to the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (SSCG).[14–16]

Data Collection

Patient data were obtained from electronic ICU medical records. Data on patient demographic characteristics, infection sites, serum IgG levels at the time of ICU admission, IVIG doses, septic shock development, length of ICU stay, ventilation days, comorbidities, blood culture positivity rate, comorbidity, admission from operating room and surgical site, admission from general ward and length of stay before ICU admission, initial reason for hospital admission, total protein, albumin levels, and 28- and 90-day mortality rates were collected. In addition, data on the requirement for renal replacement therapy (RRT) and steroid administration were collected. Sepsis severity was assessed by using the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores upon admission to the ICU. After data collection, the numbers of ICU-free days (IFDs),

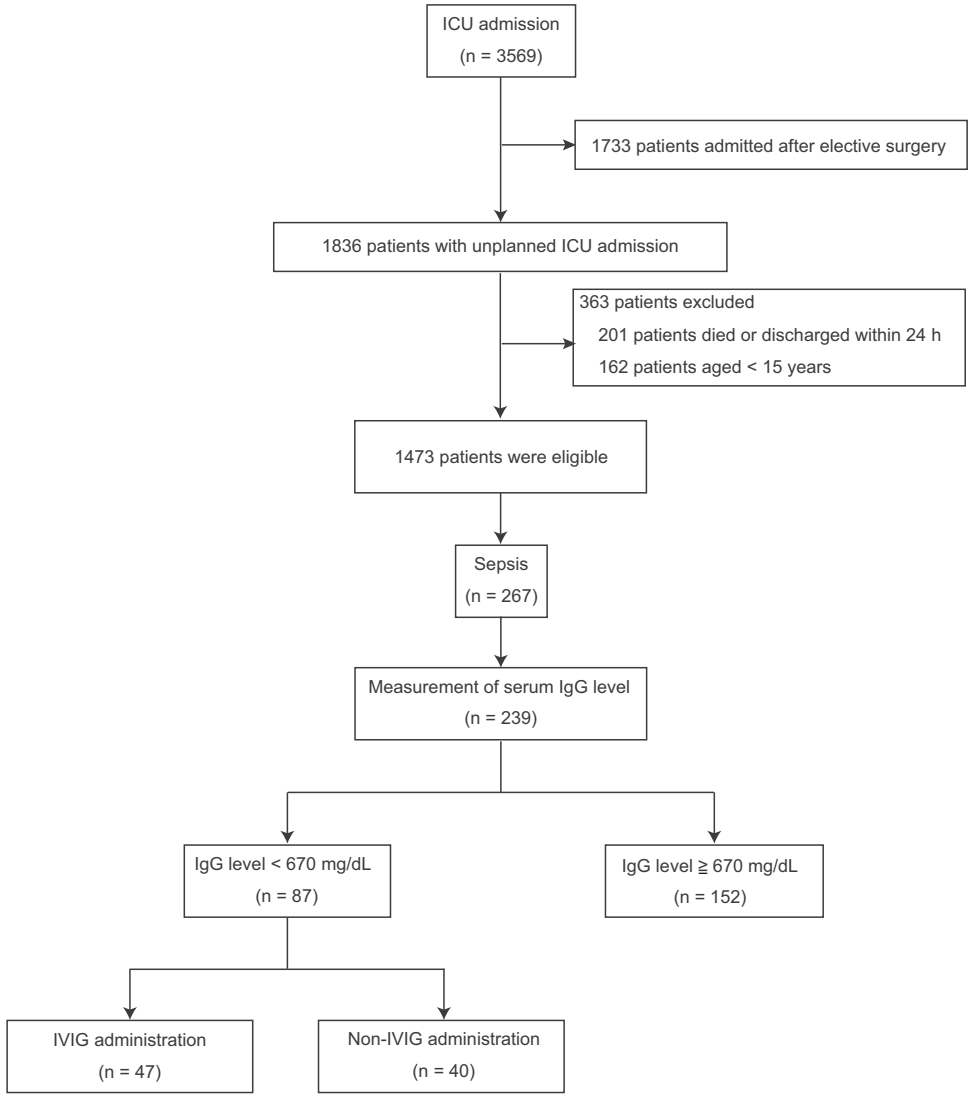

Figure 1. Flow diagram of this study. ICU = intensive care unit; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin.

ventilator-free days (VFDs), and RRT-free days (RRT-FDs) within 28 days were calculated.

Measurement of the Outcomes

The primary outcome measured was 28-day mortality. The secondary outcomes measured were IFDs, VFDs, RRT-FDs, and 90-day mortality.

Statistical Analysis

Continuous variables (age, APACHE II score, SOFA score, length of stay before ICU admission, IgG levels, total protein level, albumin level, IFDs, VFDs, and RRT-FDs) within the patients' characteristics are expressed as medians and interquartile ranges. Categorical variables (sex, infectious foci, blood culture positivity, comorbidity, admission from operating room, admission from general ward, septic shock, steroid administration, mechanical ventilation, RRT, 28-day mortality, and 90-day mortality) were analyzed by using the χ^2 test, whereas continuous variables were compared by using the Mann-Whitney *U* test.

The propensity score approach was used to address the selection bias inherent in retrospective observational studies. Propensity score was calculated by using

predicted probabilities for IVIG in logistic regression analysis using the variables age, SOFA score, immunocompromised status, and serum IgG levels, which might be expected to be associated with IVIG administration, to adjust for confounding factors. Subsequently, logistic regression analysis using propensity score as the adjusted variable was performed to determine the risk estimates for the association between IVIG therapy and primary outcome or secondary outcomes.

The 28- and 90-day mortality rates were analyzed for each group by using the Kaplan-Meier method. The survival curves obtained through the Kaplan-Meier analysis were compared by using the log-rank test. Statistical analyses were performed by using SPSS software version 27 (IBM SPSS Statistics, IBM Corporation, Armonk, New York), with statistical significance set at $P < 0.05$.

RESULTS

A flow diagram showing patient enrollment is presented in Figure 1. A total of 3569 patients were admitted to the ICU during the study period. According to the exclusion criteria, 1473 patients were eligible. Of the patients who were eligible for inclusion in this study, 267 met the Sepsis-3 criteria. Serum IgG levels were determined for 239 patients (89.5%). There were 87 (36.4%) patients who had low IgG levels (<670 mg/dL) upon admission to the ICU. The IVIG and non-IVIG groups comprised 47 and 40 patients, respectively.

Baseline Characteristics of the Patients

Age, sex, the APACHE II score, the SOFA score upon admission to the ICU, and blood culture positivity were not significantly different between the IVIG and non-IVIG groups (Table I). The cardiovascular system of SOFA scores was significantly higher in the IVIG group than in the non-IVIG group ($P = 0.01$), whereas there were no significant differences in the other 5 components of the SOFA score between the 2 groups. The predominant infectious foci were the lungs and abdomen. There were no significant differences in admission from operating room and general ward between the 2 groups ($P = 0.52$ and $P = 0.52$, respectively). Serum IgG levels in the IVIG group showed no significant difference compared with those in the non-IVIG group ($P = 0.06$). Moreover, there were no significant differences in total protein and albumin levels between the 2 groups ($P = 0.051$ and $P = 0.742$). The majority (63.8%) of patients received a 30 g supplementation dose of IVIG, whereas the rest of the patients received 15 g of IVIG. Comorbidity, shock, steroid administration, mechanical ventilation, and RRT rates were not significantly different between the groups.

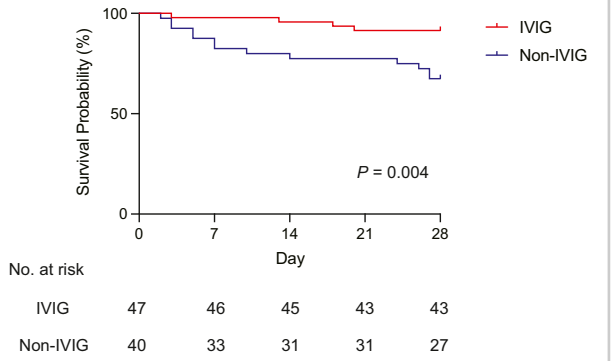

Figure 2. Kaplan-Meier survival curves up to 28 days for patients with sepsis and low immunoglobulin G (IgG) levels assigned to the intravenous immunoglobulin (IVIG) and non-IVIG groups. The red and blue lines represent patients in the IVIG and non-IVIG groups, respectively. IVIG treatment was associated with a significantly higher survival rate ($P = 0.004$).

Primary Outcome

The 28-day mortality was significantly lower in the IVIG group than in the non-IVIG group (odds ratio [OR], 0.15; 95% CI, 0.04–0.54; $P = 0.004$) (Table II). This was further supported by findings of the Kaplan-Meier survival curve analysis ($P = 0.004$) (Figure 2).

Secondary Outcomes

No significant differences in IFDs and VFDs were observed between the IVIG and non-IVIG groups. However, the number of RRT-FDs was significantly higher in the IVIG group than in the non-IVIG group (OR, 1.06; 95% CI, 1.01–1.11; $P = 0.025$). Moreover, the 90-day mortality rate was significantly lower in the IVIG group than in the non-IVIG group (OR, 0.31; 95% CI, 0.11–0.83; $P = 0.020$), which was further supported by findings of the Kaplan-Meier survival curve analysis ($P = 0.023$) (Figure 3).

Table I. Characteristics of the patients. Data are shown as median (interquartile range) or number (%) unless otherwise indicated.

Characteristic	IVIG (n = 47)	Non-IVIG (n = 40)	*P*
Age, y	69 (59–78)	64 (53–72)	0.09
Male sex	29 (61.7)	20 (50.0)	0.27
APACHE II score	21 (18–25)	23 (16–25)	0.62
SOFA score	8 (6–10)	7 (5–9)	0.39
Respiratory system	2 (1–3)	2 (1–3)	0.43
Coagulation	1 (0–3)	1(0–3)	0.94
Liver	0 (0–0)	0 (0–1)	0.08
Cardiovascular system	3 (1–4)	1 (0–3)	0.01
Nervous system	0 (0–1)	1 (0–1)	0.20
Kidney	1 (0–2)	1 (0–2)	0.16
Infectious foci, no.			0.75
Lungs	14	13	
Abdomen	16	11	
Urogenital	3	4	
Soft tissues	4	5	
Blood	0	1	
Miscellaneous	10	6	
Blood culture positivity*	12 (25.5)	16 (40.0)	0.15
Gram positive	2 (4.3)	6 (15.0)	
Gram negative	9 (19.1)	10 (25.0)	
Fungus	1 (2.1)	0 (0.0)	
Comorbidity			
Congestive heart failure	2 (4.3)	4 (10.0)	0.29
Chronic kidney disease	1 (2.1)	3 (7.5)	0.23
Diabetes mellitus	9 (19.1)	2 (5.0)	0.05
Solid tumor	19 (40.4)	9 (22.5)	0.05
Hematological	8 (17.0)	13 (32.5)	0.09
Immunocompromised status	20 (42.6)	15 (37.5)	0.63
Neurologic disorder	4 (8.5)	1 (2.5)	0.14
Admission from operating room	8 (17.0)	9 (22.5)	0.52
Surgical site			
Abdominal	7	6	
Extremities	1	3	
Admission from general ward	39 (83.0)	31 (77.5)	0.52
Length of stay before ICU admission, d	8 (1–25)	9 (1–24)	0.67
Initial reason for hospital admission, no.			
Inspection and medical treatment	13	18	
Hematopoietic stem cell transplantation	6	6	
Surgery	9	0	
Chemotherapy and/or radiotherapy	6	2	
Sepsis	5	5	
IgG level, mg/dL	441 (353–559)	517 (456–591)	0.06
Total protein level, g/dL	4.5 (4.1–5.0)	4.8 (4.4–5.2)	0.05

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Table I. (*continued*)

Characteristic	IVIG (n = 47)	Non-IVIG (n = 40)	*P*
Albumin level, g/dL	2.0 (1.8–2.3)	2.1 (1.8–2.5)	0.74
IVIG dose			
15 g	17 (36.2)	–	
30 g	30 (63.8)	–	
Shock	27 (57.4)	15 (37.5)	0.06
Steroid administration	26 (55.3)	20 (50.0)	0.62
Mechanical ventilation	38 (80.9)	26 (65)	0.15
RRT	27 (57.4)	19 (47.5)	0.42

APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive care unit; IgG = immunoglobulin G; IVIG = intravenous immunoglobulin; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.

* *Staphylococcus aureus*, 7.1%; *Enterococci*, 7.1%; *Escherichia coli*, 32.1%; *Candida*, 3.6%; coagulase-negative *Staphylococci*, 3.6%; *Klebsiella*, 14.3%; *Pseudomonas aeruginosa*, 14.3%; *Enterobacter*, 7.1%; *Parvimonas micra*, 3.6%; *Bacillus subtilis*, 3.6%; *Acinetobacter baumannii* complex, 3.6%; *Corynebacterium striatum*, 3.6%; *Bacteroides thetaiotaomicron*, 3.6%; and *Listeria monocytogenes*, 3.6%.

Table II. Odds ratios (ORs) regarding the primary and secondary outcomes in the immunoglobulin (IVIG) and non-IVIG groups. Data are shown as number (%) or median (interquartile range) unless otherwise indicated. The intensive care unit (ICU)-free and mechanical ventilation-free days were calculated according to the number of days in which the patient was alive and did not receive the specified therapy during the first 28 days after enrollment; patients who died were assigned as having 0 free days. The number of renal replacement therapy (RRT)-free days was calculated according to the number of days in which the patient did not receive RRT during the first 28 days after enrollment.

Independent Variable	IVIG Group (n = 47)	Non-IVIG Group (n = 40)	OR (95% CI)	Regression Coefficient	*P*
Primary outcome					
28-day mortality	4 (8.5)	13 (32.5)	0.15 (0.04–0.54)	−1.90	0.004
Secondary outcome					
ICU-free days for 28 days	19 (10–23)	20 (0–24)	1.02 (0.98–1.06)	0.02	0.42
Ventilator-free days for 28 days	22 (18–25)	23 (0–28)	1.02 (0.98–1.07)	0.02	0.26
RRT-free days for 28 days	25 (21–28)	25 (4–28)	1.06 (1.01-1.11)	0.05	0.025
90-day mortality	10 (21.3)	17 (42.5)	0.31 (0.11–0.83)	−1.18	0.020

DISCUSSION

Serum IgG levels are often low in infectious diseases,[17] and ~70% of critically ill patients with sepsis have low IgG levels.[18] In the present study, ~36% of patients with sepsis had low IgG levels, and the levels were lower than those reported in a previous study.[19] The definition of low IgG levels in sepsis varies across studies. Several studies have shown an association between low IgG levels and prognosis; however, different cutoff points have been used, ranging from 650 to 870 mg/dL.[18] We used IgG levels <670 mg/dL to define low IgG levels, as this level has been previously associated with poor outcomes in patients with sepsis identified by using the Sepsis-3 criteria.[12]

There are 3 possible mechanisms for low serum IgG levels during sepsis: (1) decreased production; (2) increased consumption caused by an immune response; and (3) increased extravascular distribution caused by increased vascular permeability. Taccone et al[11] examined the concentration of free light chains

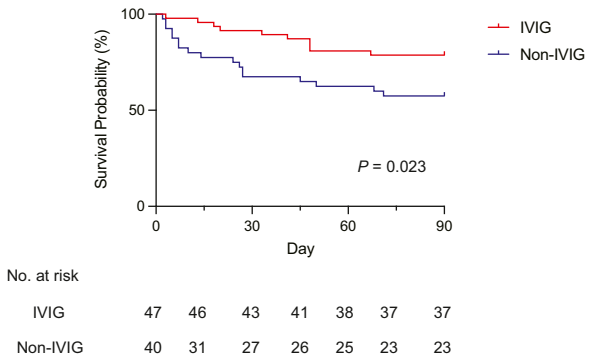

Figure 3. Kaplan-Meier survival curves up to 90 days for patients with sepsis and low immunoglobulin G (IgG) levels assigned to the intravenous immunoglobulin (IVIG) and non-IVIG groups. The red and blue lines represent patients in the IVIG and non-IVIG groups, respectively. IVIG treatment was associated with a significantly higher survival rate ($P = 0.023$).

(FLCs) produced during IgG production. The presence of FLCs is a marker for immunoglobulin synthesis, and these have a short half-life.[20] A comparison of the low and normal IgG groups at the onset of sepsis showed no significant difference in FLC levels,[11] suggesting that low IgG may not be caused by decreased immunoglobulin synthesis but rather by increased consumption or redistribution. In sepsis, the adaptive immune system is activated, antibodies against pathogenic microorganisms are produced, and a large amount of immunoglobulin is consumed to neutralize the pathogens.[21,22] Furthermore, in critically ill patients, such as those presenting with septic shock, leakage out of the vessels due to increased vascular permeability[23] may lead to a decrease in intravascular immunoglobulin concentration.

It is still controversial whether low IgG levels are associated with increased mortality in sepsis. After conducting a systematic review and meta-analysis, Shankar-Hari et al[18] reported that low IgG levels in sepsis were not associated with the risk of death. However, in a previous study,[12] patients with low IgG levels had higher mortality than those with normal IgG levels. Differences in the results among these studies may be attributed to differences in the cutoff values used to define low IgG levels (as described earlier), study design (ie, prospective or retrospective cohort studies), and/or the definition of sepsis.

In the SSCG 2016,[16] the use of IVIG for patients with sepsis or septic shock is not strongly recommended because of the low quality of supporting evidence. The SSCG 2016 was published based on high-quality literature extracted by a Cochrane systematic review with minimal bias.[4] However, most studies that were recovered using the systematic review were old RCTs conducted before the Sepsis-1 definition was established.[24] Moreover, the management of sepsis was not standardized in these studies because most of the cited RCTs were performed before the publication of the SSCG 2004.

Because the validity of IVIG therapy for sepsis is controversial, patient stratification is necessary to assess the efficacy of IVIG therapy in patients with sepsis. Because these patients with sepsis and low IgG levels may have increased mortality, IVIG supplementation for this group of patients could be an important adjunctive treatment. However, there are only a few reports on the effectiveness of IVIG therapy for sepsis management. In the present study, by analyzing recent clinical data from patients who were diagnosed by using the Sepsis-3 definition and treated with a standardized therapeutic strategy, we found that IVIG administration was associated with improved survival rate in patients with sepsis and low serum IgG levels. Further prospective studies are necessary to examine the clinical effects of IVIG therapy in patients with sepsis, depending on serum IgG levels.

In this study, we focused on patients with sepsis because this condition is life-threatening and often results in multiple organ failure. We showed that IVIG administration in patients with sepsis and low IgG levels was associated with a reduction in 28- and 90-day mortality rates. Therefore, immunoglobulin supplementation may be a viable adjunctive therapy to improve the mortality rates in patients with sepsis and low serum IgG levels. Moreover, IVIG administration was associated with an increase in RRT-FDs. Thus, this treatment strategy has the potential to promote rehabilitation in the ICU, improve the patients' quality of life in the ICU, and reduce health care costs Our results support the rationale for promoting a large-scale, multicenter, prospective study to assess the efficacy of IVIG therapy for improving the prognosis of patients with sepsis and low IgG levels.

It is important to recognize the limitations of the present study. First, serum IgG levels were not determined after IVIG administration. Therefore, it is not clear whether the serum IgG levels increased after IVIG therapy. No previous studies have measured IgG levels after IVIG and correlated these measurements with mortality. Second, this study was conducted retrospectively at a single center in a university hospital; therefore, the sample size was smaller than that of other studies. Further studies, particularly multicenter RCTs, are warranted to thoroughly investigate the effects of IVIG in patients with sepsis and low IgG levels. Third, there is the potential for selection bias in this study, as we were able to measure serum IgG levels for ~90% of the patients with sepsis because assessment of this is not available during night shifts, weekends, or holidays in our institution. Thus, ~10% of the patients "dropped out" due to the unavailability of these data. Fourth, there are no clear criteria for IVIG administration in patients with sepsis and low IgG levels. The decision to administer IVIG was made after discussion with the attending physician and intensivist in a meeting that was held twice daily at rounds. Therefore, the potential for selection bias exists. Fifth, our ICU was a surgical and medical ICU in which patients were transferred from the operating room or general ward. Therefore, some bias might exist because patients with sepsis in the emergency department were not included in our study. Lastly, different IgG subclass (IgG1–IgG4) levels were not determined. Patients may develop IgG subclass deficiencies during sepsis. Although total IgG levels may be within the normal range, subclass deficiencies might have influenced our results.

CONCLUSIONS

The present study found that IVIG treatment for patients with sepsis and low IgG levels was associated with reduced 28- and 90-day mortality rates. IVIG therapy could be a potential therapeutic option for patients with sepsis who present with low IgG levels. Prospective clinical trials should be initiated to evaluate the efficacy of IVIG therapy in a large patient population.

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Drs. Akatsuka and Masuda were responsible for conceptualization, methodology, validation, formal analysis, and project administration; Dr. Tatsumi was responsible for software; Drs. Akatsuka and Tatsumi were responsible for investigations; Drs. Akatsuka, Masuda, and Tatsumi were responsible for data curation; Drs. Akatsuka, Sonoda, and Masuda analyzed and interpreted the data; Dr. Akatsuka was responsible for writing—original draft preparation; Drs. Akatsuka, Masuda, and Tatsumi were responsible for writing—review and editing; and Dr. Masuda supervised the study. All authors read and approved the final version of the manuscript.

DISCLOSURES

Dr. Masuda received lecture fees from MSD K.K., Japan Blood Products Organization, and Asahi Kasei Corporation; and an industry-academia collaborative research grant from JIMRO Co., Ltd. Dr Tatsumi received lecture fees from TSUMURA & CO. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

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Address correspondence to: Masayuki Akatsuka, MD, PhD, Department of Intensive Care Medicine, Sapporo Medical University School of Medicine, South 1 West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan. E-mail: maasa_aka@icloud.com.