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ORIGINAL ARTICLE

Association between intravenous immunoglobulin dose and outcomes in patients with acute Kawasaki disease

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Abstract

The most effective dosage of intravenous immunoglobulin (IVIG) to prevent coronary artery abnormalities (CAAs) in patients with acute Kawasaki disease (KD) remains unknown. This study aimed to identify the appropriate dose of IVIG to be administered to patients with acute KD, using a national inpatient database in Japan. We used the Diagnostic Procedure Combination database to identify KD patients treated with IVIG between 2010 and 2020. The primary outcome was the proportion of CAAs upon discharge. Secondary outcomes included IVIG resistance, length of stay, and medical costs. Data from 88,223 patients were extracted from the database. We found a U-shaped association between IVIG dose and the proportion of CAA, with the bottom of the curve at approximately 2.0 g/kg; the odds ratio (95% confidence interval [CI]) was 1.34 (1.26–1.43) for 1.8 g/kg and 1.80 (1.29–2.51) for 2.4 g/kg with reference to 2.0 g/kg for CAA. Similarly, IVIG dose had a U-shaped association with the proportion of IVIG resistance, with the bottom of the curve at approximately 2.0 g/kg; the odds ratio (95% CI) was 1.39 (1.36–1.42) for 1.8 g/kg and 8.95 (8.15–9.83) for 2.4 g/kg with reference to 2.0 g/kg for IVIG resistance. Additionally, IVIG dosage was found to have U-shaped associations with the length of stay and medical costs, with the bottom of the curve at approximately 2 g/kg.

Conclusions: IVIG with a dose of 2 g/kg was considered appropriate for the initial treatment of KD.

What is Known:

• *For treatments of acute Kawasaki Disease (KD), IVIG has been the most recommended to reduce fever early and prevent complications of CAAs. Few studies have shown the most effective dosage of IVIG to be administered to prevent CAAs.*

What is New:

• *2 g/kg intravenous immunoglobulin was considered appropriate for the initial treatment of Kawasaki disease.*

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Keywords Kawasaki disease · Intravenous immunoglobulin · Coronary artery abnormalities · Restricted cubic spline

Abbreviations

ADL	activities of daily living
CAA	coronary artery abnormalities
CI	confidence interval
ICD-10	International Classification of Diseases, TenthRevision
IQR	interquartile range
IVIG	intravenous immunoglobulin
KD	Kawasaki Disease
SD	standard deviation
USD	United States Dollar

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis, which is the most common acquired heart disease in children from developed countries [1]. In the 1990s, a multicenter, randomized, controlled trial showed the superior effectiveness of intravenous immunoglobulin (IVIG) at 2 g/kg compared to 1.6 g/kg in managing KD; since then, 2 g/kg IVIG with aspirin has been used as the standard treatment for KD [2]. However, patients with susceptibility to infections and financial problems may need dose reduction; therefore, various trials have investigated the effectiveness of different IVIG doses for patients with acute KD [3]. Despite these trials, the most appropriate dose of IVIG remains uncertain. This study aimed to examine the association between the IVIG dose and outcomes in patients with acute KD, using a national inpatient database in Japan.

Materials and methods

Data source

This retrospective cohort study used data from the Diagnosis Procedure Combination database [4]. All 82 academic hospitals are obliged to participate in the database. Data of approximately 8 million hospitalized patients of all ages are collected annually, which is equivalent to approximately 50% of the total acute-care hospitalizations in Japan. The database includes the following information: unique identifiers of hospitals, patient characteristics, diagnosis and comorbidities at admission, and complications after admission recorded with text data in Japanese and International Classification of Diseases, Tenth Revision (ICD-10) codes. Additionally, the database contains information regarding medical treatments (including administration of drug, use of devices, and surgical and nonsurgical procedures) based on Japanese original codes, length of stay, discharge status, and medical costs during hospitalization. For the accuracy of the recorded diagnoses, the physicians in charge are obliged to record the diagnoses with reference to medical charts. Licensed medical information managers and trained medical clerks accurately record all the major and minor procedures, drugs, and devices used. Because the entry of accurate data is mandatory for reimbursement of medical costs, hospitals have a strong incentive to comply with these rules. The present study was approved by the Institutional Review Board of The University of Tokyo (approval number: 3501-(3); 25 December 2017). The requirement for informed consents was waived because of the anonymous nature of the data.

Participants

We used the database to identify patients who were diagnosed with KD (ICD-10 code: M30.3) between July 2010 and March 2020. We included patients with a history of receiving at least 1 g/kg IVIG and aspirin. We reviewed the Japanese text describing the detailed diagnoses for each patient to include atypical KD patients and exclude patients with a "suspected" diagnosis of KD. To exclude recurrence of KD, readmissions after 6 months from the initial hospitalization were excluded from the analysis. The appropriate IVIG dose for older patients with KD remains controversial [5]. We also wanted to evaluate the appropriate dose of IVIG for older children, but due to insufficient number of cases for restricted cubic spline analyses, we excluded patients older than 6 years ($N = 4378$). Furthermore, we excluded patients who weighed < 3 kg or had missing data. We classified the study population according to the IVIG dose at the initial treatment (total dose within 3 days of IVIG initiation): low-dose group, IVIG < 1.9 g/kg; standard-dose group, ≥ 1.9 ≤ 2.1 g/kg; and high-dose group, ≥ 2.1 g/kg.

Outcomes

The primary outcome was the occurrence of coronary artery abnormalities (CAAs) upon discharge. CAAs were identified with recorded diagnosis of CAAs (ICD-10 code: I25.4) and/or text data of CAAs in the Japanese language. The secondary outcomes were the proportion of IVIG resistance, duration of hospital stay, and medical costs.

The medical costs included the total price of surgery, drugs, laboratory tests, and other inpatient services, including food expense [1]. We converted 1 United States dollar (USD) to 100 Japanese yen.

IVIG resistance was defined as the use of IVIG at a total dose of ≥ 4.0 g/kg and/or combination of any steroid,

infliximab, cyclosporine, and/or plasma exchange that were not given during the initial IVIG treatment.

Covariates

The patient characteristics included sex, age, weight, height, hospital days of illness at the initial IVIG treatment, use of 10% IVIG, initial steroid use, initial cyclosporine use, hospital type, complex chronic conditions [6], Japan Coma Scale at admission, transportation by ambulance, transportation from other hospitals, fiscal year, and hospital volume. Initial steroid use and initial cyclosporine use were defined as use concurrent with initial IVIG. In Japan, all medical expenses for patients in this age group are covered by public funds, so there is no possibility of changing the dosage of IVIG for financial reasons. For the hospital type, academic hospital was defined as university hospital and related hospitals. A previous study confirmed the correlation between the Japan Coma Scale and the Glasgow Coma Scale [7]. Hospital volume was defined as the number of new KD patients at each hospital annually. The patients were divided into tertiles according to hospital volume to equalize the number of patients in each group.

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using the Fisher exact test. Continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR). Non-normally distributed variables (length of stay and medical costs) were compared among three groups using the Kruskal–Wallis test. In the sensitivity analysis for CAA, CAAs were defined as a diagnosis of CAAs plus the use of anticoagulants, such as warfarin or clopidogrel, or a diagnosis of CAAs by cardiac catheterization.

Restricted cubic spline functions

Studies regarding the relationship between the IVIG dose and outcomes converted continuous measures of IVIG into categorical variables. However, this might result in loss of information and decrease in statistical power [8]. Therefore, we used multivariable regression models with restricted cubic spline functions to assess the potential non-linear association of IVIG dose with CAA, IVIG resistance, length of stay, and medical cost. Multivariable logistic regression models were applied for CAA and IVIG resistance, and multiple regression models were applied for length of stay and medical cost with adjustment for age, sex, body weight, body height, hospital days of illness at the initial IVIG treatment, use of 10% IVIG, initial steroid use, initial cyclosporine use, type of hospital, complex chronic conditions, transportation by ambulance, Japan Coma Scale at admission, transportation from other hospital, fiscal year, and hospital volume. We created restricted cubic splines with five knots at pre-specified locations according to the percentiles of the distribution of IVIG doses (1.8, 2.0, 2.2, 2.4, and 2.6 g/kg).

Tests for overall and non-linear associations were performed using the χ^2 test [9]. A two-sided value of $p < 0.05$ was considered significant. Statistical analyses were performed using the Stata software version 17 (StataCorp LP, TX, USA).

Results

Patient characteristics are shown in Table 1. Initially, 88,223 patients with acute KD were identified using the inclusion criteria (Fig. 1). The mean age was 1.9 (SD, 1.6) years, and the mean body weight was 11.8 (3.7) kg; among the 88,223 patients, 50,438 (57.2%) were male. The median total amount of IVIG was 2.05 (IQR, 1.97–2.36) g/kg. Regarding the initial IVIG dose, the low-dose group ($n = 12{,}777$) had a median of 1.87 (IQR, 1.79–2.08) g/kg, the standard-dose group ($n = 46{,}558$) had a median of 2.00 (IQR, 1.97–2.05) g/kg, and the high-dose group ($n = 28{,}888$) had a median of 3.00 (IQR, 2.17–4.06) g/kg ($p < 0.001$). Moreover, 10% IVIG and initial cyclosporine were used more frequently in the high-dose and low-dose groups, respectively. CAA and IVIG resistance occurred in 973 (1.1%) and 20,421 (23.1%) patients, respectively. The median (IQR) of length of stay and medical costs were 10 (8.0–13.0) days and 6471 (5314–8193) USD, respectively.

Compared with the low- and high-dose groups, the standard-dose group showed the lowest proportions of CAA (0.7%, $p < 0.001$) and IVIG resistance (12.7%, $p < 0.001$), the shortest length of stay (median 9 days, $p < 0.001$), and the lowest medical costs (median, 6,145 USD; $p < 0.001$) (Table 2).

The sensitivity analysis for CAA was performed, in which CAA was confirmed in 189 patients (0.2%) among whole patients. As in the main analysis, the standard dose group showed the lowest proportion of CAA (0.1%, $p < 0.001$).

Regarding restricted cubic spline functions, tests for overall association and non-linear association showed significant results for CAAs, IVIG resistance, length of stay, and medical costs, indicating a significant non-linear relationship between IVIG dose and outcomes. A U-shaped association was observed between IVIG dose and CAA proportion, with the bottom of the curve at approximately 2.0 g/kg; the odds ratio (95%

Table 1 Patient characteristics

Variables	Total ($n=88,223$)	Low-dose group ($n=12,777$)	Standard-dose group ($n=46,558$)	High-dose group ($n=28,888$)	p value
Age, mean (SD), years	1.9 (1.6)	1.7 (1.6)	2.1 (1.7)	1.8 (1.6)	<0.001
Male (%)	50,438 (57.2%)	7359 (57.6%)	26,486 (56.9%)	16,593 (57.4%)	0.19
Weight, mean (SD), kg	11.8 (3.7)	11.6 (3.8)	12.2 (3.7)	11.2 (3.6)	<0.001
Height, mean (SD), cm	75.4 (31.9)	74.8 (30.7)	76.6 (32.1)	73.7 (32.0)	<0.001
Hospital days of illness at initial IVIG, median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	<0.001
Total amount of initial IVIG, median (IQR), g/kg	2.027 (1.957–2.152)	1.807 (1.424–1.869)	2.000 (1.966–2.041)	2.344 (2.158–3.125)	<0.001
Use of 10% IVIG	9687 (11.0%)	1286 (10.1%)	4360 (9.4%)	4041 (14.0%)	<0.001
Initial steroid use	9480 (10.7%)	1432 (11.2%)	5141 (11.0%)	2907 (10.1%)	<0.001
Initial cyclosporine use	183 (0.2%)	75 (0.6%)	64 (0.1%)	44 (0.2%)	<0.001
Type of hospital					
Academic hospital	15,338 (19.3%)	2448 (21.2%)	7879 (18.8%)	5011 (19.4%)	<0.001
Complex chronic conditions					
0–1	84,860 (96.2%)	12,241 (95.8%)	44,987 (96.6%)	27,632 (95.7%)	<0.001
2≤	3363 (3.8%)	536 (4.2%)	1571 (3.4%)	1256 (4.3%)	
Transportation by ambulance	2013 (2.3%)	432 (3.4%)	875 (1.9%)	706 (2.4%)	<0.001
Japan coma scale					
Alert	87,527 (99.2%)	12,674 (99.2%)	46,251 (99.3%)	28,602 (99.0%)	<0.001
Not alert	696 (0.8%)	103 (0.8%)	307 (0.7%)	252 (0.9%)	
Transportation from other hospital	67,299 (76.3%)	9741 (76.2%)	35,671 (76.6%)	21,887 (75.8%)	0.028
Hospital volume					
Low (1.0–29.7)	28,430 (32.2%)	4310 (33.7%)	14,792 (31.8%)	9328 (32.3%)	<0.001
Middle (29.8–56.2)	30,307 (34.4%)	4454 (34.9%)	15,825 (34.0%)	10,028 (34.7%)	
High (≥56.3)	29,486 (33.4%)	4013 (31.4%)	15,941 (34.2%)	9532 (33.0%)	

ADL activities of daily living, *IQR* interquartile range, *IVIG* intravenous immunoglobulin, *SD* standard deviation

confidence interval [CI]) was 1.34 (1.26–1.43) for 1.8 g/kg and 1.80 (1.29–2.51) for 2.4 g/kg compared to 2.0 g/kg. Similarly, a U-shaped association was observed between the IVIG dose and IVIG resistance proportion, with the bottom of the curve at approximately 2.0 g/kg; the odds ratio (95% CI) was 1.39 (1.36–1.42) for 1.8 g/kg and 8.95 (8.15–9.83) for 2.4 g/kg compared to 2.0 g/kg. Additionally, IVIG dose was found to have U-shaped associations with length of stay and medical costs, with the bottom of the curve at approximately 2 g/kg. The difference (95% CI) in the length of stay was 1.02 (0.98–1.05) days for 1.8 g/kg and 2.20 (2.01–2.39) days for 2.4 g/kg with reference to 2 g/kg. The difference in medical costs was 543.9 (522.7–565.0) USD for 1.8 g/kg and 2326 (2218–2434) USD for 2.4 g/kg compared to 2 g/kg (Figs. 2, 3, 4 and 5).

In the sensitivity analysis for CAA, a U-shaped association was observed between IVIG dose and CAA proportion, with the bottom of the curve at approximately 2.0 g/kg; the odds ratio (95% CI) was 1.33 (1.17–1.52) for 1.8 g/kg and 2.33 (1.18–4.61) for 2.4 g/kg compared to 2.0 g/kg (Fig. 6).

Discussion

This study used restricted cubic spline functions to evaluate the association between IVIG dose and outcomes. The lowest CAA, IVIG resistance, length of stay, and medical costs were observed at a dose of approximately 2 g/kg.

In the 1980s, various treatments were applied for patients with acute KD; similarly, IVIG doses and administration methods varied [10, 11]. Newburger's study led to the increased popularity of using a dose of 2 g/kg IVIG worldwide [2]. However, several studies have tried to use various doses of IVIG for treating acute KD patients, and their results showed no significant difference in the proportion of CAAs between the various IVIG doses [3, 12–14]. This might be due to the small sample sizes of their studies. No previous study has examined the most appropriate dose of IVIG; therefore, the present study is the first to show that 2 g/kg IVIG could be the most appropriate for the management of patients with acute KD.

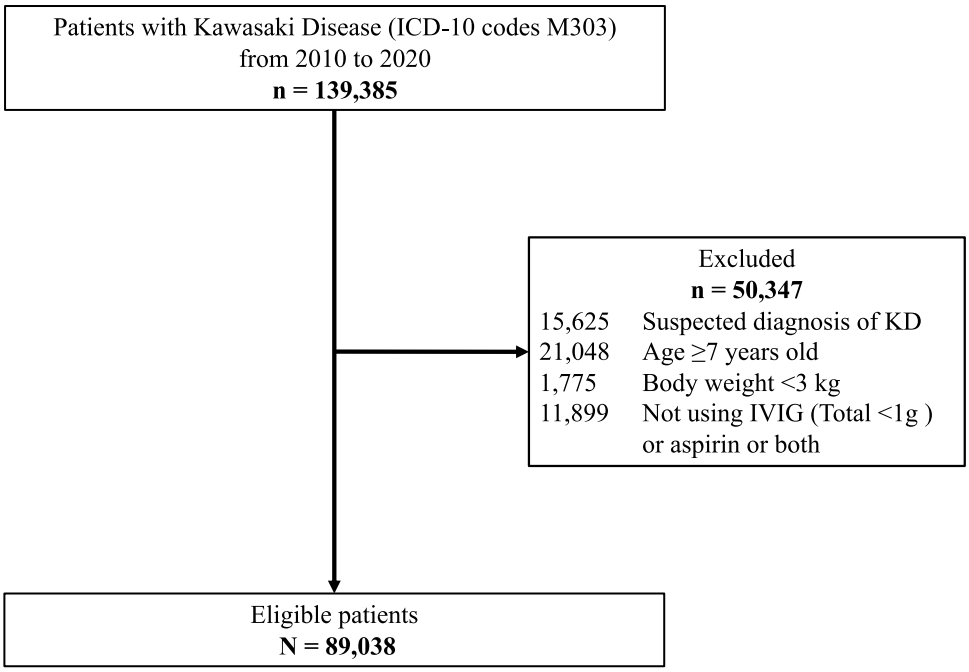

Fig. 1 Flow chart for the study cohort. ICD-10, International Classification of Diseases, Tenth Revision; IVIG, intravenous immunoglobulin; KD, Kawasaki disease

In this study, the effect of a dose of > 2 g/kg IVIG on the incidence of CAA was not clearly shown. A previous study emphasized that increased heart failure risk was due to volume overload of IVIG in patients with acute KD [15]. An excessive dose of IVIG may increase the risk of heart failure, and the shear stress of the coronary artery, resulting in CAA. Considering this, the incidence of CAA may increase at IVIG doses > 2 g/kg; however, the effect remains unknown. This study suggests that an IVIG dose of 2 g/kg may be sufficient to reduce inflammation in acute KD; on the contrary, IVIG doses < 2 g/kg may be insufficient to suppress inflammation in acute KD, resulting in increased CAAs, IVIG resistance proportions, length of stay, and medical costs.

IVIG is an expensive preparation, the cost of which further increases with an increased dose. Patients with IVIG resistance and additional IVIG treatment usually undergo longer lengths of stay and higher medical costs.

Additionally, IVIG is a blood product, so its infusion may cause infections. In the current manufacturing process of plasma fractionation products, it is difficult to completely inactivate or remove viruses, such as human parvovirus B19. To avoid this risk and the increase in medical costs, it is important to use the appropriate dose of IVIG. In this context, the present study results suggest that IVIG 2 g/kg should be recommended to treat KD patients in the acute phase.

Limitations

This study has several limitations. First, our database lacked data regarding KD symptoms, laboratory findings, and fever

Table 2 Comparison of outcomes among three groups with different doses of IVIG

	Low-dose group (n = 12,777)	Standard-dose group (n = 46,558)	High-dose group (n = 28,888)	p value
Proportion of CAAs (%)	276 (2.2)	349 (0.7)	348 (1.2)	< 0.001
Proportion of IVIG resistance (%)	2775 (21.7)	5,892 (12.7)	11,754 (40.7)	< 0.001
Length of stay (day)	10 (8–14)	9 (8–12)	11 (8–13)	< 0.001
Medical cost (USD)	6250 (5002–8390)	6145 (5183–7348)	7448 (5825–9709)	< 0.001
Proportion of CAAs (sensitivity analysis**) (%)	77 (0.6)	47 (0.1)	65 (0.2)	< 0.001

CAAs coronary artery abnormalities, *IVIG* intravenous immunoglobulin, *USD* United States dollars

*All data are presented as medians (interquartile ranges)

**CAA in the sensitivity analysis was defined as diagnosis of CAA only (the main analysis) plus drug therapy (warfarin or clopidogrel) and/or cardiac catheterization

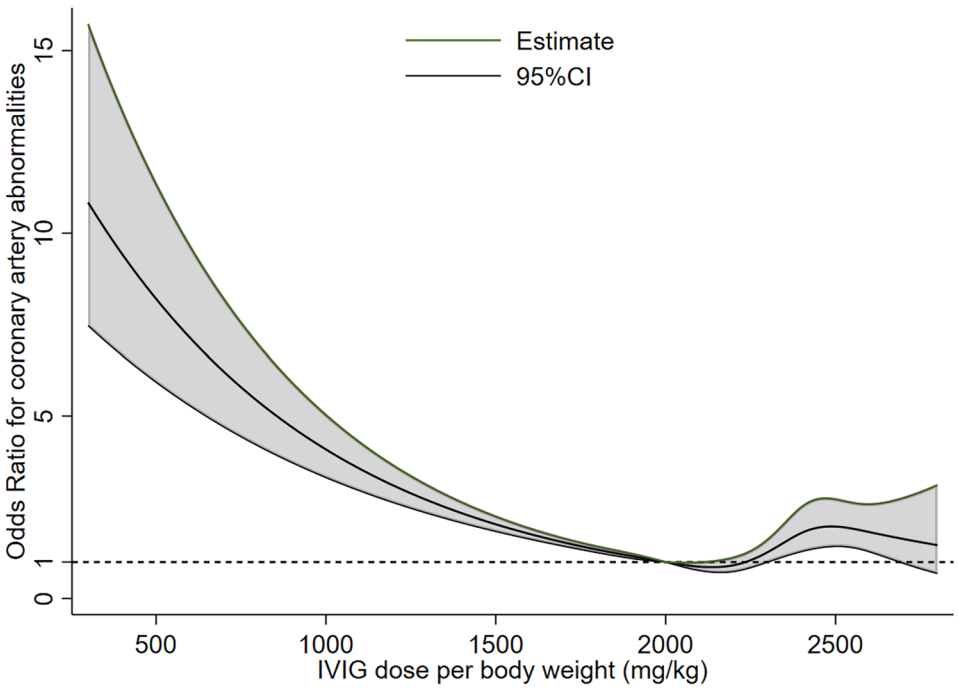

Fig. 2 Restricted cubic spline for coronary artery abnormalities. The dose–response relationship between intravenous immunoglobulin dose and proportion of coronary artery abnormalities was adjusted by analysis using a restricted cubic spline with five knots (IVIG, 1.8, 2.0, 2.2, 2.4, and 2.6 g/kg). The graphs show the estimated values along with 95% CI. IVIG, intravenous immunoglobulin; CI, confidence interval

duration of patients with acute KD. It is impossible to know "Days of illness" at the time the patient was admitted from our database; therefore, we used "Hospital days of illness." Second, the severity of CAAs due to KD, expressed as coronary arterial diameters or *Z* scores, was not included in our database. To clarify that CAAs were not transient, we used the history of cardiac catheterization and the prescription history of anticoagulants in addition to aspirin. Third, the accurate clock time of IVIG administration, observation time, and duration of fever in patients with KD could not be evaluated from the database. Fourth, the initial dose of IVIG was recorded within 3 days of the start of IVIG administration, which might not correctly capture the initial amount of IVIG used in the analysis and might capture patients in

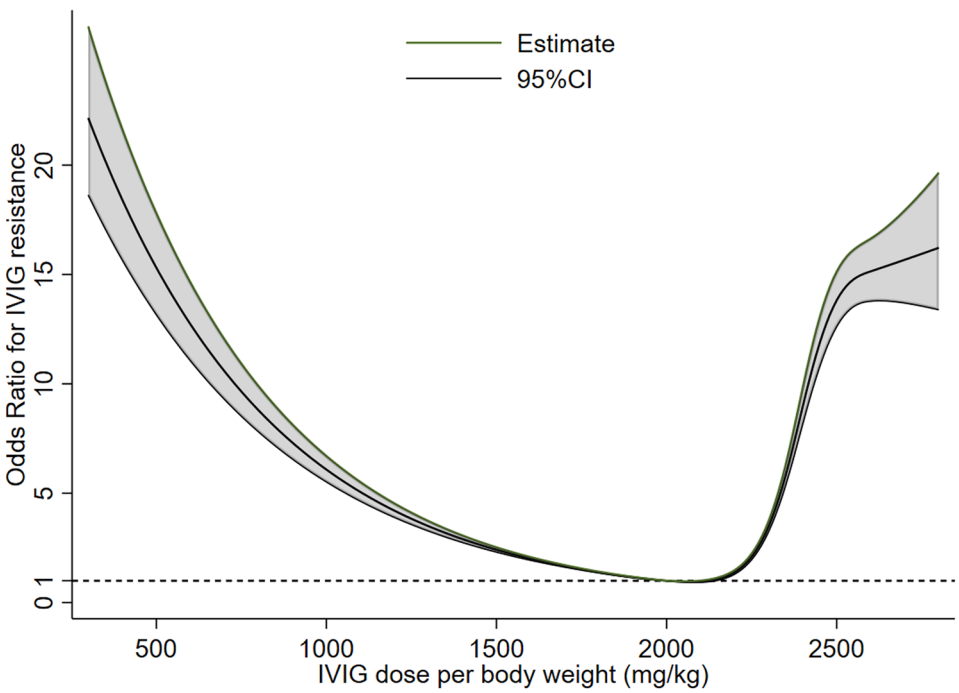

Fig. 3 Restricted cubic spline for intravenous immunoglobulin resistance. The dose–response relationship between intravenous immunoglobulin dose and proportion of intravenous immunoglobulin resistance was adjusted by analysis using a restricted cubic spline with five knots (IVIG, 1.8, 2.0, 2.2, 2.4, and 2.6 g/kg). The graphs show the estimated values along with 95% CI. IVIG, intravenous immunoglobulin; CI, confidence interval

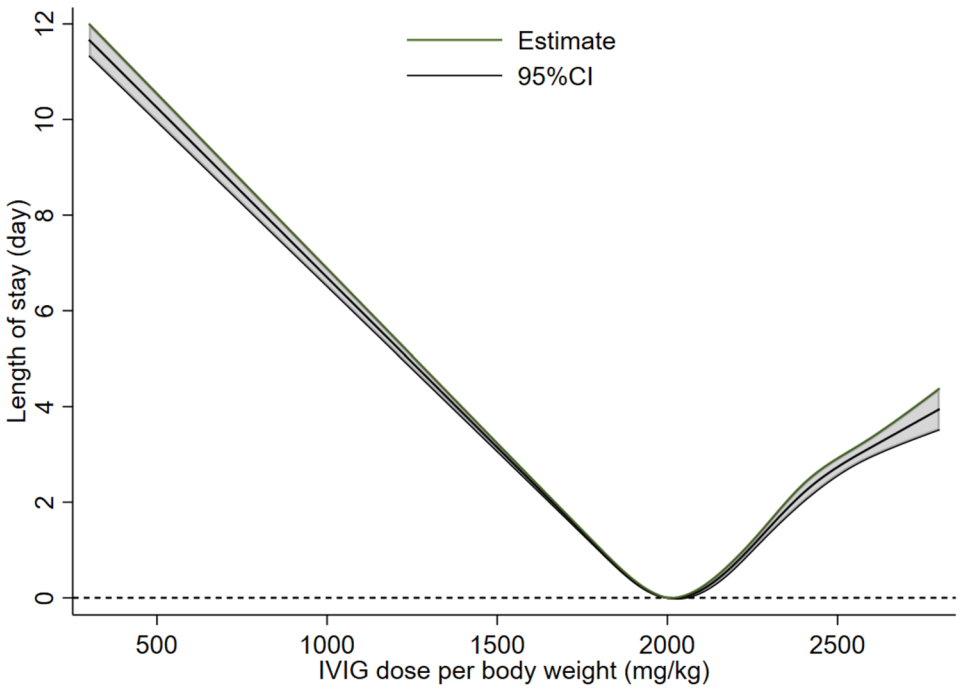

Fig. 4 Restricted cubic spline for length of stay. The dose–response relationship between intravenous immunoglobulin dose and the length of stay was adjusted by analysis using a restricted cubic spline with five knots (IVIG 1.8, 2.0, 2.2, 2.4, and 2.6 g/kg). The graphs show the estimated values along with 95% CI. IVIG, intravenous immunoglobulin; CI, confidence interval

the high-dose group in their second IVIG therapy cycle. We chose the duration of "within 3 days", because the initial IVIG treatment usually requires 1–2 days with an additional 1–2 days to assess patients' responses. The high proportion of IVIG resistance of more than 40% in the high-dose group was a limitation partly because of this definition. This might have prevented a clear analysis of the final result of IVIG resistance. Fifth, the results of this study were limited to the age and weight distributions of the population studied, because this study evaluated only the appropriate IVIG dose for typical KD patients, and patients older than 6 years and weighing less than 3 kg were excluded.

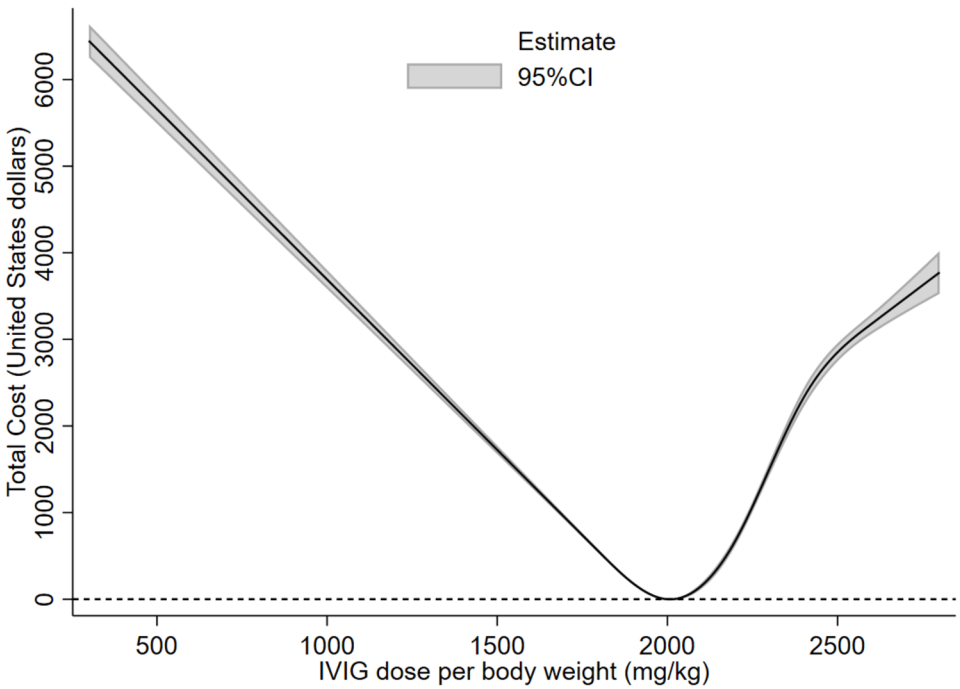

Fig. 5 Restricted cubic spline for total medical cost. The dose–response relationship between intravenous immunoglobulin dose and total medical cost was adjusted by analysis using a restricted cubic spline with five knots (IVIG 1.8, 2.0, 2.2, 2.4, and 2.6 g/kg). The graphs show the estimated values along with 95% CI. IVIG, intravenous immunoglobulin; CI, confidence interval

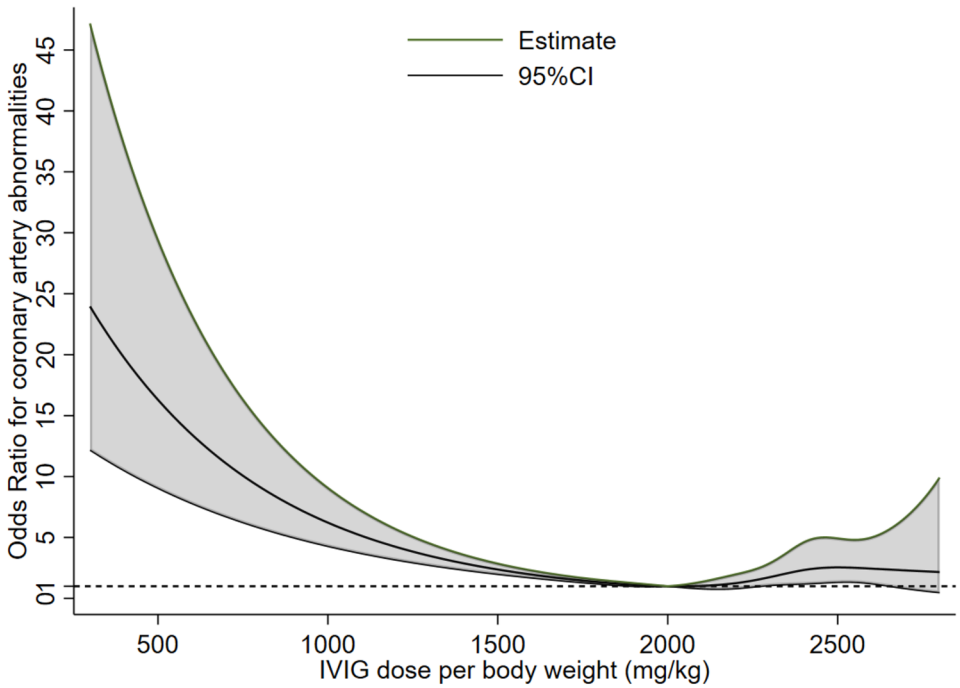

Fig. 6 Restricted cubic spline for coronary artery abnormalities in the sensitivity analysis. The dose–response relationship between intravenous immunoglobulin dose and proportion of coronary artery abnormalities in the sensitivity analysis was adjusted by analysis using a restricted cubic spline with five knots (IVIG 1.8, 2.0, 2.2, 2.4, and 2.6 g/kg). The graphs show the estimated values along with 95% CI. IVIG, intravenous immunoglobulin; CI, confidence interval

Conclusion

The study results show that IVIG 2 g/kg is the most appropriate dose for treating KD patients. Prospective studies are required to confirm the conclusion of this study.

Author contributions NM wrote the first draft of the manuscript. TS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. KS, TY, HM, KF, and HY conceptualized and designed the study, and coordinated and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and material The datasets analyzed during the current study are not publicly available due to contracts with the hospitals providing data to the database.

Code availability This study was analyzed using the standard packages of the Stata software version 16.1 (StataCorp LP, College Station, TX, USA).

Declarations

Conflict of interest disclosures All authors have no potential conflicts of interest to disclose.

Ethics approval The present study was approved by the Institutional Review Board of The University of Tokyo (approval number: 3501-(3); 25 December 2017).

Consent to participate The requirement for informed consents was waived because of the anonymous nature of the data.

Consent for publication This paper isn't included an individual's data or image.

Open access We do not want open access.

Article summary This study showed by restricted cubic spline that the dose of intravenous immunoglobulin for Kawasaki disease in acute phase was 2g/kg.

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