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# Initial intravenous immunoglobulin therapy without aspirin for acute Kawasaki disease: a retrospective cohort study with a Bayesian inference

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## ABSTRACT

**Objective** To clarify the necessity of acetylsalicylic acid (ASA) administration combined with intravenous immunoglobulin (IVIG) therapy in the treatment of acute Kawasaki disease.

**Design** Retrospective cohort study.

**Setting** Multicentre.

**Participants** This study included 735 patients with Kawasaki disease aged ≤10 years and hospitalised between 4 and 10 days of illness in eight Japanese hospitals from January 2016 to December 2020.

**Exposures** High-dose (HD) ASA was administered with initial IVIG to 333 patients in 6 hospitals (HD group). ASA was not administered routinely to 402 patients in the other two hospitals, and low-dose ASA was only administered when patients developed coronary artery lesions or pericardial effusion (non-HD group).

**Primary and secondary outcome measures** The primary outcome was the presence of coronary artery lesions, defined as a coronary artery diameter >+2.5 SD of body surface area within 1 month of onset. The secondary outcome was responsiveness to the initial IVIG therapy. Adjusted risk ratios for the outcomes were calculated using modified Poisson regression models. Bayesian analysis was conducted to estimate the posterior probability of the treatment effect of HD ASA under several prior distributions.

**Results** The incidence of coronary artery lesions was not significantly higher in the HD group than in the non-HD group (12/333 (3.6%) vs 15/402 (4.0%)). The proportion of non-responders to initial IVIG was similar between the two groups (HD group: 78/333 (23%); non-HD group: 83/402 (22%)). In the Bayesian analysis, considering a difference of ≤2% to be of no clinical importance, there was only a 9.3% chance of reduced risk of coronary artery lesions in the HD group compared with the non-HD group even with a strongly enthusiastic prior for HD treatment.

**Conclusions** Compared with HD ASA treatment, treatment without ASA in the acute phase of Kawasaki disease was not associated with increased complications from Kawasaki disease.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the acute phase of Kawasaki disease, medium-dose to high-dose acetylsalicylic acid is concomitantly administered with intravenous immunoglobulin. However, the efficacy of acetylsalicylic acid administration in the treatment of Kawasaki disease complications is controversial.

### WHAT THIS STUDY ADDS

⇒ Zero acetylsalicylic acid administration during the acute phase of Kawasaki disease did not significantly elevate the risk of complications compared with the administration of high-dose acetylsalicylic acid.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study findings suggest the reconsideration of current guidelines recommending the administration of acetylsalicylic acid in acute Kawasaki disease.

## INTRODUCTION

Kawasaki disease (KD) is a disease of unknown aetiology that causes vasculitis of small-sized to medium-sized arteries such as the coronary artery. Coronary artery lesions (CALs) develop in 15%–25% of children with untreated KD[1]; moreover, KD remains a leading cause of acquired heart disease in children. Kusakawa *et al* reported that acetylsalicylic acid (ASA), as a treatment for the acute phase of KD, might have a better effect on reducing CALs than flurbiprofen and prednisolone plus dipyridamole.[2] In addition, Koren *et al* demonstrated the efficacy of high-dose (HD) ASA in shortening the febrile period of KD.[3] Originally, Furusho *et al* showed that intravenous immunoglobulin (IVIG) therapy alone was superior to HD ASA therapy for KD[4]; however, HD ASA was concomitantly administered with IVIG therapy.

ASA has antiplatelet and anti-inflammatory effects. Low-dose ASA (3–5 mg/kg/day) inhibits cyclooxygenase (COX)-1 and exerts antiplatelet effects. HD ASA (80–100 mg/kg/day) is believed to be necessary for inhibiting COX-2 and inducing anti-inflammatory effects.

Recently, some studies have reported negative results regarding the anti-inflammatory effects of HD ASA. Dallaire *et al* reported that low-dose ASA was not inferior to HD ASA in reducing the incidence of CALs.[5] Four meta-analyses revealed that low-dose ASA had treatment outcomes similar to those of HD ASA, particularly on CAL-related morbidity.[6–9] In addition, ASA results in rare but possibly severe side effects such as bleeding, Reye's syndrome,[10] liver dysfunction and hearing loss.[11] The Japanese KD guidelines recommend the administration of medium-dose ASA (30–50 mg/kg/day), considering the hepatic vulnerability of Japanese people to ASA.[12] Hence, the efficacy of ASA administration during IVIG therapy for patients with KD, especially in the prevention of CALs, remains controversial.

ASA may not reduce KD complications and may further increase its adverse effects. Few studies have compared HD ASA to no antiplatelet treatment as the initial treatment for KD; these studies showed non-superiority of HD ASA to no antiplatelet treatment.[13–16] A systematic review confirming the efficacy of ASA in the treatment of KD did not provide sufficient evidence to determine whether the omission of antiplatelets from KD treatment provided equivalent treatment outcomes.[17] Therefore, this multicentre retrospective cohort study aimed to investigate whether a no-ASA treatment modality could affect the treatment outcomes of KD such as the incidence of CALs or unresponsiveness to initial IVIG.

## METHODS

### Study design and setting

This multicentre retrospective cohort study of patients with KD explored the effects of ASA in the acute phase of KD. Eight hospitals with different treatment policies for ASA administration were included. In six hospitals, HD ASA (targeted 30–50 mg/kg/day) was concomitantly administered with initial IVIG. In the remaining two hospitals, ASA was not routinely administered and low-dose ASA (3–5 mg/kg/day) was administered only when patients developed CALs or pericardial effusion. This study adhered to the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology. There was no patient and/or public involvement in this research.

### Participants

Medical records of the participating hospitals were reviewed, and patients diagnosed with acute KD and hospitalised between January 2016 and December 2020 were identified. Patients diagnosed after 2021 were excluded because there many paediatric patients were infected with SARS-CoV-2 in Japan after 'the fourth wave' (July to September 2021).

This study included patients if (1) they were aged ≤10 years, (2) they presented with at least four of the six principal features (fever, change in extremities, polymorphous exanthema, conjunctival injection, changes in the lips and oral cavity and cervical lymphadenopathy) and (3) the initial IVIG treatment started between days 4 and 10. Patients were excluded if the size of their coronary arteries was >+2.0 SD[18] at the time of diagnosis or if a corticosteroid was administered alongside the initial IVIG. Patients with a history of haemodynamically significant structural heart disease or KD were excluded.

### Exposure

The primary exposure status was defined according to the administration of ASA at the time of initial IVIG treatment. Patients who received ASA >10 mg/kg/day were categorised as the HD group; those who did not receive ASA at all or received ASA <10 mg/kg/day were categorised as the non-HD group. Patients who were administered antiplatelet drugs other than ASA (eg, flurbiprofen) were excluded.

### Outcomes and covariates

This study's primary outcome was the presence of CALs, including transient dilatation of the coronary arteries, within 1 month of disease onset. Patients were considered to present with CALs when two-dimensional echocardiography showed that internal lumen diameters were >2.5 SD for body surface area, or there were apparent aneurysmal changes in the coronary artery in the medical records. Generally, the echocardiogram was performed at least at the time of diagnosis, within 48 hours after diagnosis and initial treatment, and approximately 10 days after disease onset, although it should be noted that these intervals were not predetermined. The secondary outcome was responsiveness to the initial IVIG treatment. Patients were defined as refractory to the initial IVIG treatment if they received a second-line treatment such as additional IVIG with or without systemic corticosteroid administration or other immunosuppressive therapies.

The following data were collected immediately before the initial IVIG treatment: white cell count, percentage of neutrophils, haematocrit, platelet (PLT) count and serum concentrations of C reactive protein (CRP), sodium, aspartate aminotransferase (AST), alanine aminotransferase, total bilirubin and albumin.

### Sample size

This study was considered an exploratory observational study; however, the sample size was calculated assuming it was a non-inferior trial. Based on previous studies,[19] the incidence probability of the primary outcome was expected to be 15%; the inferior margin was set to 7.5%. With a one-sided type I error of 10% and a power of 80%, a sample size of 205 patients per group was required to

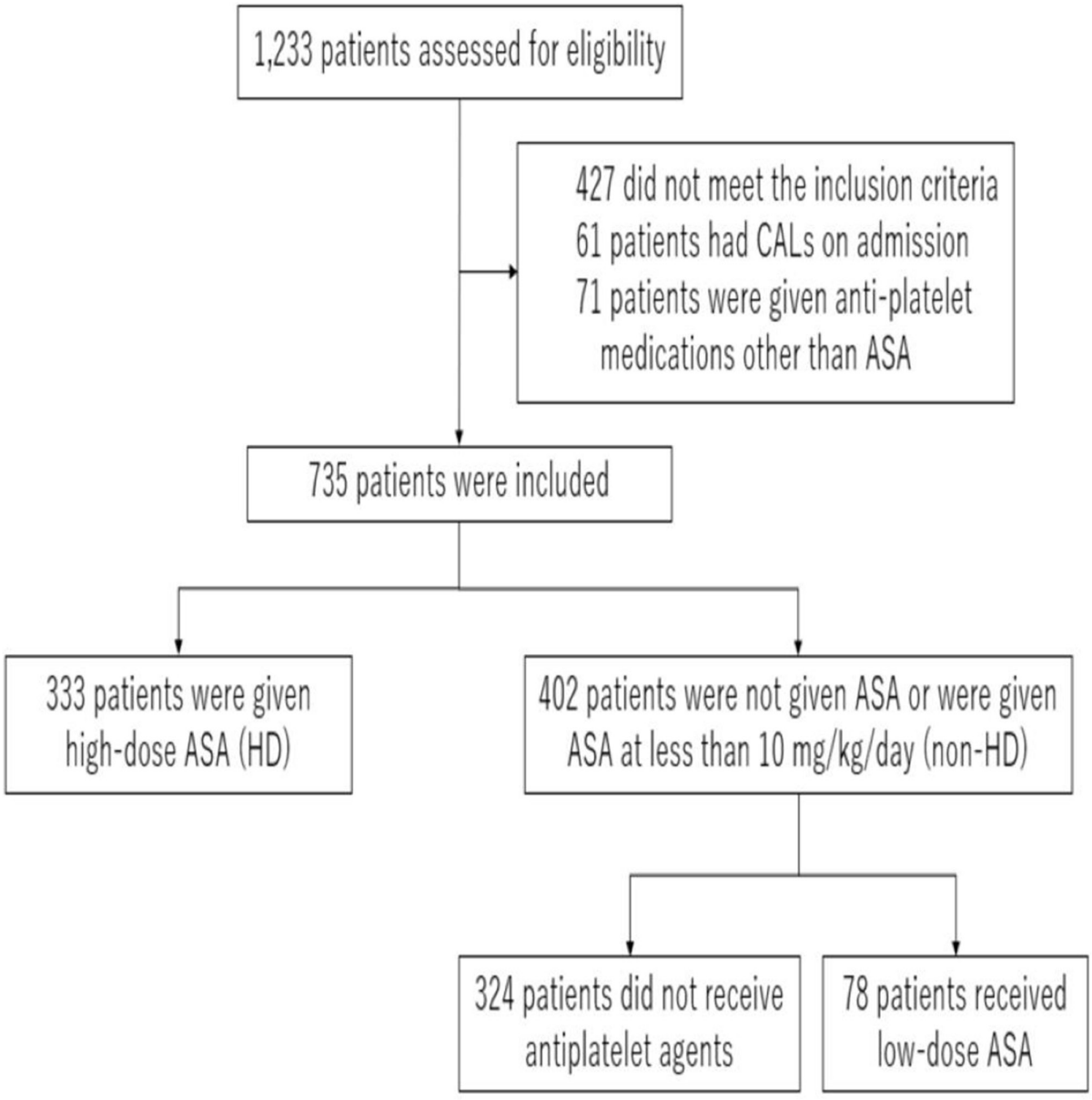


**Figure 1** Patient flow. ASA, acetylsalicylic; CALs, caronary artery lesions; HD, high dose; IVIG, intravenous immunoglobulim.

detect non-inferiority. A target sample size of 230 patients per group was determined assuming a 10% drop-out rate.

### Statistical analysis

Patient characteristics are summarised as numbers and percentages for categorical variables and means and SD for continuous variables. The adjusted risk ratios (aRRs) for the outcomes were calculated using modified Poisson regression models with robust variance estimator including the following covariates: age, sex, clinical day of initial IVIG treatment, percentage neutrophil count, and PLT, CRP, sodium, and AST levels. Variables, except for sex, were selected on the Kobayashi score,[20] which is widely recognised as a high-risk indicator for the development of CALs in KD. As patients at high risk of developing CALs could be more likely prescribed with ASA, these variables were included as potential cofounders. In the regression analysis, the Wald test was used to obtain two-tailed p values, and a $p<0.05$ was considered statistically significant.

We also implemented propensity score matching and inverse probability of treatment weighting (IPTW). The propensity score was estimated using a logistic regression model including the above-mentioned covariates. We conducted one-to-one matching without replacement using a calliper width of 0.2 of SD of the logit of the propensity score. Using the matched cohort, the risk ratio was calculated using the Mantel-Haenszel method. In IPTW approach, the weights were stabilised, and the risk ratios were obtained using the modified Poisson regression models.

**Table 1** Patient characteristics

| | Overall (N=735) | HD group (N=333) | Non-HD group (N=402) | P value |
|---|---|---|---|---|
| Background | | | | |
| Age | 2 (1–3) | 2 (1–3) | 2 (1–3) | 0.64 |
| Male sex | 419 (58.9%) | 200 (60.1%) | 219 (57.9%) | 0.57 |
| Kobayashi score | 3 (1–4) | 3 (1–5) | 2 (1–4) | 0.004 |
| Predicted as IVIG non-responder | 157 (22.0%) | 85 (25.5%) | 72 (19.0%) | <0.001 |
| Clinical day of IVIG | 5 (5–6) | 5 (4–6) | 5 (5–6) | 0.004 |
| Duration from onset to afebrile | 6 (5–7) | 6 (5–7) | 5.5 (5–7) | 0.31 |
| Duration from treatment to afebrile | 1 (1–2) | 2 (1–2) | 1 (1–2) | <0.001 |
| Second-line treatment | | | | |
| Add second-line treatment | 161 (22.6%) | 78 (23.4%) | 83 (22%) | 0.81 |
| Second-line treatment | | | | 0.04 |
| IVIG+PSL | 21 (13.0%) | 4 (5.1%) | 17 (20.5%) | |
| IVIG only | 135 (83.9%) | 72 (92.3%) | 63 (75.9%) | |
| PSL only | 3 (1.9%) | 2 (2.6%) | 1 (1.2%) | |
| Other | 2 (1.2%) | 0 (0.0%) | 2 (2.4%) | |
| Coronary artery lesions (CALs) | | | | |
| CALs within 1 month (>+2.5 SD) | 27 (3.8%) | 12 (3.6%) | 15 (4.0%) | <0.001 |
| CALs within 1 month (5 to <10 SD) | 7 (1.0%) | 4 (1.2%) | 3 (0.8%) | <0.001 |
| CALs within 1 month (≥10 SD) | 2 (0.3%) | 0 (0.0%) | 2 (0.5%) | <0.001 |
| CALs over 1 month (>+2.5 SD) | 10 (1.4%) | 6 (1.8%) | 4 (1.1%) | 0.54 |
| CALs over 1 year (>+2.5 SD) | 2 (0.3%) | 0 (0.0%) | 2 (0.5%) | 0.56 |
| Complications other than CALs | | | | |
| ALT elevation | 33 (4.6%) | 10 (3.0%) | 23 (6.1%) | 0.08 |
| Gall bladder swelling | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | >0.99 |
| Gastrointestinal ulcer | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | >0.99 |
| Arthritis | 3 (0.4%) | 1 (0.3%) | 2 (0.5%) | >0.99 |
| Seizure | 6 (0.8%) | 2 (0.6%) | 4 (1.1%) | 0.86 |
| Facial nerve palsy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | >0.99 |
| Carditis | 1 (0.1%) | 0 (0.0%) | 1 (0.3%) | >0.99 |
| ALT elevation within 2 months | 2 (0.3%) | 1 (0.3%) | 1 (0.3%) | >0.99 |
| Laboratory findings | | | | |
| White cell count ($10^9$/L) | 13.3 (10.5–16.6) | 13.95 (11.3–17.0) | 13.0 (10.1–16.2) | 0.003 |
| % of Neutrophil | 67.25 (57–77) | 67.5 (58.4–77.2) | 67 (54–77) | 0.27 |
| Haematocrit | 33.9 (32.1–35.7) | 34.15 (32.1–35.9) | 33.8 (32.1–35.5) | 0.32 |
| Platelet count ($10^9$/L) | 343 (277–403) | 345 (284–400) | 341 (274–406) | 0.62 |
| Albumin (g/dL) | 3.6 (3.3–3.8) | 3.6 (3.3–3.8) | 3.5 (3.3–3.8) | 0.12 |
| C reactive protein (mg/dL) | 7.3 (4.4–11.2) | 7.6 (4.7–11) | 7.1 (3.82–11.28) | 0.54 |
| AST (IU/L) | 34 (26–55.5) | 33 (25–59) | 34 (26–55) | 0.12 |
| ALT (IU/L) | 21 (12–82) | 23 (13–83) | 21 (12–81.5) | 0.95 |
| Total bilirubin (mg/dL) | 0.5 (0.4–0.8) | 0.5 (0.4–0.8) | 0.5 (0.4–0.7) | 0.53 |
| Serum Na (mEq/L) | 135 (133–136) | 134 (132–136) | 135 (133–137) | 0.007 |

Data are presented as median (IQR) or number (percentage).
ALT, alanine aminotransferas; AST, aspartate aminotransferase; HD, high dose; IVIG, intravenous immunoglobulin; PSL, prednisolone.

As a sensitivity analysis, we conducted a Bayesian analysis[21] in which prior information based on our knowledge was combined with the present data to update the belief on the treatment effect of ASA. The aim of this analysis was to assess the clinical impact of HD ASA, particularly in populations believed to have a lower risk of CALs that included children aged between 3 months and 10 years with a low Kobayashi score (4 points). This targeted approach was also intended to mitigate the potential variability in criteria for initiating IVIG treatment across different institutions. By varying the degree of clinician belief

Table 2 Results of multivariable analysis for the risk of developing coronary artery lesions within 1 month

| | Regression analysis | | | | Propensity score analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | Matching | | IPTW | |
| | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value |
| HD | (Reference) | | (Reference) | | (Reference) | | (Reference) | |
| Non-HD | 1.27 (0.97 to 1.67) | 0.08 | 1.12 (0.83 to 1.51) | 0.46 | 1.44 (0.62 to 3.38) | 0.40 | 1.19 (0.90 to 1.56) | 0.23 |
| Age (year) | – | | 0.39 (0.27 to 0. 56) | <0.001 | – | | – | |
| Male | – | | 1.11 (0.75 to 1.07) | 0.61 | – | | – | |
| Clinical day of IVIG | – | | 1.48 (1.20 to 1.81) | <0.001 | – | | – | |
| Serum Na (mEq/L) | – | | 0.98 (0.93 to 1.03) | 0.46 | – | | – | |
| AST (IU/L) | – | | 1.00 (1.00 to 1.00) | <0.001 | – | | – | |
| % of Neutrophil | – | | 1.05 (1.03 to 1.07) | <0.001 | – | | – | |
| Platelet count ($10^9$/L) | – | | 1.00 (0.99 to 1.00) | 0.07 | – | | – | |
| C reactive protein (mg/dL) | – | | 1.04 (1.01 to 1.07) | 0.012 | – | | – | |

AST, aspartate aminotransferase; HD, high dose; IPTW, inverse probability of treatment weighting; IVIG, intravenous immunoglobulin.

in the efficacy of ASA, we aimed to validate its potential therapeutic significance. We assumed the following model:

n_HD~Binomial (θ_HD, N_HD).

n_non-HD~Binomial (θ_non-HD, N_non-HD).

θ_HD~Beta (80 920).

θ_non-HD~Beta (α,β).

where n is the number of patients who developed CALs within 1 month among N patients in each group. The parameter θ represents the probability of developing CALs, which was assumed to have a beta distribution.

Based on a national survey of patients with KD in Japan,[22] the reference prior to the distribution of the HD group was assumed to be a beta distribution with parameters of 80 and 920, which was equivalent to the evidence that 80 of 1000 patients developed CALs. For the priors of the non-HD group (θ_non-HD), four different distributions were set to represent the researchers' scepticism or enthusiasm for using HD ASA treatment: (1) a minimally informative prior (α=1/2, β=1/2), which represents no prior belief about how much likely CALs develop in the non-HD group, (2) a sceptical prior (α=80, β=920), which corresponds to a belief that the risk of CALs in the non-HD group is 8% in a trial of 1000 patients similar to the reference prior in the HD group, (3) moderately enthusiastic (α=88, β=912) and (4) strongly enthusiastic (α=96, β=904) priors, which were equivalent to a trial that 1000 patients in the non-HD group showed 1.1 and 1.2 higher risk of CALs than did the HD group, respectively. These prior beliefs were updated using data from patients aged between 3 months and 10 years with a low Kobayashi score (≤4 points) and were not considered to be at a high risk of developing CALs.

Four separate sampling sequences were set, each consisting of 1000 random samples (including 500 samples discarded for convergence). Sampling convergence was evaluated using Gelman-Rubin statistics and by visually inspecting a trace plot. Among 2000 samples (4 chains with 500 samples in each), we counted samples in which the posterior probability of developing CALs in the non-HD group (θ_non-HD) was higher than that in the HD group (θ_HD) by several degrees of clinical importance ϕ (0%, 1%, 2% and 3%), which was analogous to the risk difference with various inferior margins ϕ. R software V.4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses. The probabilistic programming language Stan (Stan Development Team) was used for the Bayesian analysis.

## RESULTS

### Participant characteristics

Of the 1233 eligible patients, 806 without missing data necessary for inclusion were registered (figure 1).

Table 3 Results of multivariable analysis for unresponsiveness to IVIG

| | Regression analysis | | | | Propensity score analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | Matching | | IPTW | |
| | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value | Risk ratio (95% CI) | P value |
| HD | (Reference) | | (Reference) | | (Reference) | | (Reference) | |
| Non-HD | 1.04 (0.92 to 1.19) | 0.50 | 1.09 (0.92 to 1.29) | 0.30 | 1.08 (0.81 to 1.45) | 0.60 | 1.09 (0.94 to 0.26) | 0.25 |
| Age (year) | – | | 1.03 (0.97 to 1.08) | 0.31 | – | | – | |
| Male | – | | 1.22 (1.08 to 1.38) | <0.001 | – | | – | |
| Clinical day of IVIG | – | | 0.83 (0.74 to 0.94) | 0.002 | – | | – | |
| Serum Na (mEq/L) | – | | 0.94 (0.91 to 0.98) | <0.001 | – | | – | |
| AST (IU/L) | – | | 1.00 (1.00 to 1.00) | <0.001 | – | | – | |
| % of Neutrophil | – | | 1.02 (1.01 to 1.03) | 0.001 | – | | – | |
| Platelet count ($10^9$/L) | – | | 1.00 (1.00 to 1.00) | <0.001 | – | | – | |
| C reactive protein (mg/dL) | – | | 1.02 (1.01 to 1.03) | <0.001 | – | | – | |

Additionally, online supplemental tables S2 an S3 summarise the results of the multivariable analysis for the risk of developing CALs and unresponsiveness to the initial IVIG treatment based on the use of low-dose ASA within the non-HD group.
ASA, acetylsalicylic acid; AST, aspartate aminotransferase; CALs, coronary artery lesions; HD, high dose; IPTW, inverse probability of treatment weighting; IVIG, intravenous immunoglobulin.

Sixty-one patients with CALs on admission were excluded. Additionally, 71 patients who were administered antiplatelet medications other than ASA were excluded. The registration forms for some patients who did not satisfy the inclusion criteria were incomplete; therefore, the precise reason for their exclusion was unknown. Finally, 735 patients were included in this analysis.

Of the 735 patients, 333 were administered HD ASA. Among the 402 patients not administered with HD ASA, 324 did not receive antiplatelet agents and 78 received low-dose ASA. Table 1 shows the baseline characteristics of the patients and their outcomes. Additionally, online supplemental table S1 presents a detailed comparison of patient characteristics based on the use of low-dose ASA within the non-HD group.

### Multivariable regression and propensity score analysis

Table 2 summarises the results of the multivariable analysis for the risk of developing CALs. Compared with the HD group, the aRR in the non-HD group was 1.12 (95% CI 0.83 to 1.51). In the propensity score analyses, neither the matching nor the IPTW approach revealed a statistically significant difference between the HD and non-HD groups despite a higher point estimate being observed. The distribution of propensity score and the balanced of covariates before and after matching are shown in online supplemental figure S1.

Table 3 shows that there was no significant difference in unresponsiveness to the initial IVIG treatment between the non-HD and HD groups (aRR 1.09; 95% CI 0.92 to 1.29).

### Bayesian analysis

In the Bayesian analysis, we used the data of patients at low risk of developing CALs (age, 3 months to 10 years; Kobayashi score ≤4 points); 8 of the 204 (3.9%) patients in the HD group and 7 of the 307 (2.3%) patients in the non-HD group developed CALs. The posterior probability distributions with four different priors are graphically shown in online supplemental figure S2. The posterior probability distribution with a minimally informative prior (online supplemental figure S2A) showed a higher incidence of CALs in the HD group, demonstrating that the incidence of CALs in the HD group was higher than that in the non-HD group based on the data used. Even with a moderately enthusiastic prior belief for HD treatment, the risk of developing CALs in the non-HD group was 10% higher, and the posterior probability of both groups was similarly distributed (online supplemental figure S2C).

Table 4 summarises the posterior probability that the incidence of CALs in the non-HD group was higher than that in the HD group by a certain degree $\phi$ (0%, 1%, 2% and 3%), which demonstrates clinical importance. For example, a probability of $(\theta_{non} - \theta_{HD})$ >2% implies the likelihood that non-HD treatment, compared with HD treatment, increases the risk of developing CALs by >2%. If we consider that a difference of ≤2% is not of clinical

Table 4 Difference between posterior probability in the HD and non-HD groups

| Reference prior for the HD treatment | >0 | >1% | >2% | >3% |
|---|---|---|---|---|
| Minimally informative | 0.0% | 0.0% | 0.0% | 0.0% |
| Sceptical (RR=1.0) | 27.8% | 5.3% | 0.5% | 0.0% |
| Moderately enthusiastic (RR=1.1) | 49.7% | 16.9% | 3.2% | 0.1% |
| Strongly enthusiastic (RR=1.2) | 69.0% | 34.6% | 9.3% | 1.1% |

HD, high dose; RR, risk ratio.

importance (ie, an inferior margin of 2%), there was only a 9.3% chance that HD treatment reduced the risk of CALs than did non-HD treatment, even with a strongly enthusiastic belief for HD treatment. The results using the minimally informative prior were all 0% because it is essentially equivalent to judgement based solely on the data.

## DISCUSSION

HD ASA exerts anti-inflammatory effects by inhibiting COX-2. In contrast, low-dose ASA inhibits COX-1 and exerts an antiplatelet effect. ASA is 170-fold less effective at inhibiting COX-2 than it is at inhibiting COX-1.[23] Therefore, there is a difference in the dosage required to obtain each effect. Before the administration of IVIG for KD, HD ASA was used for KD treatment because of its anti-inflammatory effects. However, some studies have not shown the superiority of HD ASA over low-dose ASA in terms of the incidence of CALs.[6–9 24] In this study, the majority of patients in the non-HD group (80.5%; 324/402) did not receive ASA, while 54 patients received low-dose ASA after the initial IVIG treatment owing to the development of CALs or pericardial effusion. The no-ASA modality showed non-inferiority to routinely administered HD ASA with respect to the incidence of CALs.

In addition, this study conducted a Bayesian analysis to estimate the posterior probability of the treatment effect of HD ASA under various reference priors. Even with a strongly enthusiastic prior for HD treatment that the risk ratio of CALs was 1.2 in the non-HD group compared with the HD group, this study showed the posterior probability that HD superiority was only 69.0%. This analysis showed that this study's results are considered robust, even though clinicians strongly prefer HD ASA.

Regarding the proportion of unresponsiveness to initial IVIG therapy, there was no inferiority in the non-HD group compared with the HD group, which is consistent with the results of previous studies and meta-analyses.[5 7–9 14 16] The duration from treatment to the absence of fever was significantly shorter in the non-HD group than in the HD group; this result is contrary to that of two previous studies.[14 25] ASA may cause various adverse events. Regarding the adverse events associated with ASA, abdominal discomfort is the most common, and the incidence of liver dysfunction was 0.9%.[26] Although this study found no significant difference in the frequency of adverse events between both groups, the sample size might not have been large enough. It is uncertain whether low-dose to medium-dose ASA causes severe adverse effects related to ASA; hence, the risks of administering ASA should be considered.

This study had several limitations. First, this was a retrospective observational study, which was not the optimal design for evaluating non-inferiority. Additionally, there was no pre-established protocol for treatment and evaluation methods within and between facilities, potentially introducing bias or residual confounders related to this lack of standardisation. To address these limitations, we employed several analytical methods, including Bayesian analysis, to validate the conclusions drawn. While the subjectivity of a Bayesian approach provides readers with greater interpretative flexibility, it might also leave room for interpretative arbitrariness. Second, this study included only patients with KD who presented with at least four principal features and began treatment after 4 days of illness. Patients who started receiving treatment before meeting the KD criteria and those who might be at a high risk of developing CALs were excluded; this may explain why CAL-related morbidity in this study was lower than that reported previously.[21] However, comparability across different institutions was prioritised, making lower generalisability inevitable. Third, long-term outcomes were not assessed. While the effects of ASA therapy in KD might warrant evaluation from a medium-term to long-term perspective, our study lacked sufficient data on long-term prognoses. Although Kato *et al* reported a 49.3% regression rate for coronary aneurysms within 1–2 years,[27] the decreased incidence of cases presenting with coronary aneurysms in the modern era means that our study's sample size was inadequate for outcomes related to aneurysm regression or long-term coronary aneurysm persistence. Fourth, 24 patients in the non-HD group were administered low-dose ASA before initial IVIG. Compared with patients who were not administered ASA throughout the acute phase, those patients tended to be younger and had a higher Kobayashi score; this could lead to an indication bias, although adjusting for possible confounders yielded the same result.

In conclusion, this study revealed that the no-ASA modality in the acute phase of KD was non-inferior to HD ASA administration with respect to the incidence of CALs. This study suggests that the KD guidelines recommending ASA administration in the acute phase of KD should be revised.

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## REFERENCES

1 Newburger JW, Takahashi M, Gerber MA, *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on rheumatic fever, Endocarditis and Kawasaki disease, Council on cardiovascular disease in the young, American heart Association. *Circulation* 2004;110:2747–71.
2 Kusakawa S, Tatara K. Research on treatment of acute-stage Kawasaki disease (the 2ND report): A prospective study of three treatment options: aspirin, Flurbiprofen, Prednisolone+Dipyridamole. *J Jpn Pediatr Soc* 1985;89:814–8.
3 Koren G, Rose V, Lavi S, *et al*. Probable efficacy of high-dose salicylates in reducing coronary involvement in Kawasaki disease. *JAMA* 1985;254:767–9.
4 Furusho K, Kamiya T, Nakano H, *et al*. Intravenous gamma-globulin for Kawasaki disease. *Acta Paediatr Jpn* 1991;33:799–804.
5 Dallaire F, Fortier-Morissette Z, Blais S, *et al*. Aspirin dose and prevention of coronary abnormalities in Kawasaki disease. *Pediatrics* 2017;139:e20170098.
6 Ho LGY, Curtis N. What dose of aspirin should be used in the initial treatment of Kawasaki disease *Arch Dis Child* 2017;102:1180–2.
7 Zheng X, Yue P, Liu L, *et al*. Efficacy between low and high dose aspirin for the initial treatment of Kawasaki disease: Current evidence based on a meta-analysis. *PLoS One* 2019;14:e0217274.
8 Chiang MH, Liu HE, Wang JL. Low-dose or no aspirin administration in acute-phase Kawasaki disease: a meta-analysis and systematic review. *Arch Dis Child* 2021;106:662–8.
9 Jia X, Du X, Bie S, *et al*. What dose of aspirin should be used in the initial treatment of Kawasaki disease? A meta-analysis. *Rheumatology (Oxford)* 2020;59:1826–33.
10 Wei C-M, Chen H-L, Lee P-I, *et al*. Reye's syndrome developing in an infant on treatment of Kawasaki syndrome. *J Paediatr Child Health* 2005;41:303–4.
11 Scuccimarri R. Kawasaki disease. *Pediatr Clin North Am* 2012;59:425–45.
12 Research Committee of the Japanese Society of Pediatric Cardiology, Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease. Guidelines for medical treatment of acute Kawasaki disease: report of the research committee of the Japanese society of pediatric cardiology and cardiac surgery (2012 revised version). *Pediatr Int* 2014;56:135–58.
13 Hsieh K-S, Weng K-P, Lin C-C, *et al*. Treatment of acute Kawasaki disease: aspirin's role in the febrile stage Revisited. *Pediatrics* 2004;114:e689–93.
14 Lee G, Lee SE, Hong YM, *et al*. Is high-dose aspirin necessary in the acute phase of Kawasaki disease *Korean Circ J* 2013;43:182–6.
15 Nakada T. Effects of anti-inflammatory drugs on intravenous immunoglobulin therapy in the acute phase of Kawasaki disease. *Pediatr Cardiol* 2015;36:335–9.
16 Kuo H-C, Lo M-H, Hsieh K-S, *et al*. High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. *PLoS One* 2015;10:e0144603.
17 Tanoshima R, Hashimoto R, Suzuki T, *et al*. Effectiveness of antiplatelet therapy for Kawasaki disease: a systematic review. *Eur J Pediatr* 2019;178:947–55.
18 Kobayashi T, Fuse S, Sakamoto N, *et al*. A new Z score curve of the coronary arterial internal diameter using the Lambdamu-Sigma method in a pediatric population. *J Am Soc Echocardiogr* 2016;29:794–801.
19 Nakamura Y, Yashiro M, Uehara R, *et al*. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005-2006. *Journal of Epidemiology* 2008;18:167–72.
20 Kobayashi T, Inoue Y, Takeuchi K, *et al*. Prediction of intravenous immunoglobulin Unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113:2606–12.
21 Quintana M, Viele K, Lewis RJ. Bayesian analysis: using prior information to interpret the results of clinical trials. *JAMA* 2017;318:1605–6.
22 Makino N, Nakamura Y, Yashiro M, *et al*. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015-2016. *Pediatr Int* 2019;61:397–403.
23 Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* 1998;38:97–120.
24 Baumer JH, Love SJL, Gupta A, *et al*. Salicylate for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2006;2006:CD004175.
25 Kim GB, Yu JJ, Yoon KL, *et al*. Medium- or higher-dose acetylsalicylic acid for acute Kawasaki disease and patient outcomes. *The Journal of Pediatrics* 2017;184:125–129.
26 Huang X, Huang P, Zhang L, *et al*. Is aspirin necessary in the acute phase of Kawasaki disease *J Paediatr Child Health* 2018;54:661–4.
27 Kato H, Sugimura T, Akagi T, *et al*. Long-term consequences of Kawasaki disease. A 10- to 21- year follow-up study of 594 patients. *Circulation* 1996;94:1379–85.