Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original Article

Cost-effectiveness analysis of infliximab for the treatment of Kawasaki disease refractory to the initial treatment: A retrospective cohort study

Tomoyuki Takura (PhD), Sayaka Horiuchi (MD) *

Department of Healthcare Economics and Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

ARTICLE INFO

Article history:
Received 28 December 2021
Received in revised form 4 February 2022
Accepted 7 March 2022
Available online xxxx

Keywords:
Mucocutaneous lymph node syndrome
Infliximab
Intravenous immunoglobulin
Cost-effectiveness analysis

ABSTRACT

Background: Infliximab (IFX) treatment is approved in Japan for health insurance coverage in patients with Kawasaki disease (KD). This study aimed to compare the cost-effectiveness of IFX and other therapeutic strategies for KD refractory to initial treatment, including intravenous immunoglobulin (IVIG), steroids, immunosuppressants, and plasma exchange therapy.

Methods: This multicenter, retrospective cohort study utilized data from the public medical insurance system of Japan. The target population included those who received treatment for KD between April 2012 and March 2019. Eligibility criteria were as follows: 1) initial onset of KD, 2) age < 15 years at onset, and 3) administration of 3rd line treatment if the 1st line treatment was IVIG alone or 2nd line treatment if the 1st line treatment was a combination of IVIG and steroids, in accordance with Japanese guidelines (2012). Those with KD-related cardiovascular complications before admission and those with congenital cardiac disease were excluded. The primary outcome was cost-effectiveness, which was calculated based on the number of admission events per annum divided by medical expenses per annum (times/10,000 US dollars). The Wilcoxon test was applied to analyze the difference in cost-effectiveness between patients who had received IFX and those who had not.

Results: Among 1267 patients with KD, 25 received IFX treatment, while 206 received another treatment after the disease was designated refractory to initial treatment. The frequency of steroid use during initial IVIG treatment (a predictor of severity) was higher in the non-IFX group than in the IFX group (70.4% vs. 32.0%, $p < 0.001$) but became comparable after propensity-score matching. Our analysis indicated that IFX was more cost-effective than other treatments [1.04 (0.86, 1.34) vs. 1.38 (1.03, 1.79) (times/10,000 US dollars), $p = 0.006$].

Conclusions: IFX treatment may be more cost-effective than non-IFX treatment for patients with KD that is refractory to initial treatment.

Introduction

Kawasaki disease (KD) is a vasculitis syndrome specific to children that mainly affects small- and medium-sized arteries. Cardiac sequelae such as coronary artery aneurysm (CAA), which occurs in 2–3% of patients treated for KD [1], can lead to significant morbidity or even mortality [2,3]. However, CAA can be prevented by suppressing inflammation early in acute phase treatment.

Initiation of intravenous immunoglobulin (IVIG) (2 g/kg) within 10 days of fever onset has been confirmed to reduce the risk of CAA by approximately 20% (from 25% to <5%) [4–8]. High-dose IVIG (2 g/kg) or combination with steroid therapy as 1st line treatment has reduced rates of cardiac sequelae in Japan [9]. However, approximately 20% of cases remain refractory to 1st line treatment [1]. Refractory cases have been associated with a higher risk of cardiac sequelae than that observed in responders, with studies reporting that 48.6–54.0% of patients with refractory KD may develop CAA [10,11]. Therefore, selection of additional treatments that can suppress inflammation is important in refractory cases.

In 2015, the Japanese health insurance system began covering IFX for the treatment of KD, leading to increases in its use for refractory cases [12,13]. Several studies have reported that additional IVIG [14], steroid [14], immunosuppressant [15], and plasma exchange [16,17] treatments are effective in preventing cardiovascular complications in patients with KD refractory to initial treatment, respectively. However, few studies have compared the effectiveness of these strategies in refractory cases with that of monoclonal antibodies or anti-cytokine biologics, including IFX. A 2019 systematic review that investigated 2nd line therapy in patients with IVIG-refractory KD reported no differences in coronary outcomes, although they noted that IFX significantly reduced the duration of fever when compared with IVIG or steroids [18].

* Corresponding author at: Department of Healthcare Economics and Health Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan.
E-mail address: sayakahoriuchi@gmail.com (S. Horiuchi).

https://doi.org/10.1016/j.jjcc.2022.03.005

Another study reported that IFX may shorten the duration of hospitalization and consequently reduce medical costs when compared with a second IVIG treatment for refractory KD [19].

Previous studies have suggested the potential superiority of IFX over other treatments in terms of cost-effectiveness. However, it remains inconclusive whether IFX is more effective in reducing CAA than other therapeutic options. Given the reduced incidence of CAA [9], conducting a clinical trial to evaluate the effectiveness of each treatment in preventing CAA would not be feasible. Moreover, in real-world settings, additional treatment for refractory cases may be more complex. Therefore, it is necessary to evaluate the effectiveness of overall treatment for refractory KD during the acute phase in a real-world setting rather than in an "ideal" clinical trial setting. The actual benefit of treatment options should be discussed in terms of both clinical gain and medical expenses [20].

Therefore, in the present study, we aimed to compare the cost-effectiveness of IFX and its effectiveness in reducing cardiovascular complications with that of non-IFX options for the treatment of KD refractory to initial treatment using real-world data.

Methods

Study design and setting

This multicenter retrospective longitudinal cohort study involved the use of a large database that includes medical service data examined by a specialized public organization (Social Insurance Medical Fee Payment Fund), in accordance with the format stipulated by the Ministry of Health, Labour, and Welfare (MHLW Notification: Vol. 0831 No. 1). We selected medical economic big data (*TheBD*: The Tokyo University Health Economy Big Data, Supplementary material and the database overview (Online Table 1)) [20,21], which included medical service bills gathered from public insurers (including health insurance societies of companies) throughout Japan between April 2012 and March 2019, representing coverage for 7 million insured patients.

As for the sample composition by year, 2016 accounted for the largest proportion (22.1% of the total). Medical information accounted for 6.18 million results, while dispensing information accounted for 6.20 million results (including duplications). The patient-based hospitalization rate was 13.5% (including duplications), and the average percentage of male patients for all years was 46.8%. This database is updated every 6 months. All data on disease name, testing, medication, surgery, any other medical interventions with dates of initiation and related costs are linked in chronological order using unique IDs for each patient. During each biannual update, transfer of data for insured persons is managed, and adjustments are made according to relocation of medical facilities. *TheBD* has been used in several studies that have evaluated the economic aspects of medical interventions (Supplementary material and the database overview (Online Table 1)).

Study participants

The study included patients with KD who had received additional treatment for KD that was considered refractory to initial treatment. Refractory cases are typically defined based on the presence of persistent or recurrent fever following completion of the initial treatment. However, *TheBD* does not include data related to fever. Therefore, refractory cases of KD were identified based on the receipt of additional treatment for KD in accordance with the "Clinical Guideline for Medical Treatment of Acute Stage Kawasaki Disease (2012)" during the same episode of admission, under the assumption that patients with fever would receive necessary additional treatment in Japan [22]. According to the guidelines (2012), IFX is recommended as 3rd line treatment if the 1st line treatment was IVIG alone or as 2nd line treatment if the 1st line treatment was combination therapy with IVIG and steroids.

The eligibility criteria were as follows: 1) initial onset of KD with an ICD-10 code of M30.3, a code that corresponds to the pathological condition of KD; 2) age under 15 years at the time of onset; and 3) administration of 3rd line treatment if the 1st line treatment was IVIG alone or 2nd line treatment if the 1st line treatment was a combination of IVIG and steroids.

Exclusion criteria were as follows: 1) recurrent KD, 2) existence of coronary/cardiovascular complications prior to admission, and 3) congenital cardiac disease.

The study participants were extracted from *TheBD* by using age at the time of medical consultation, main disease name (ICD-10 code), and medical treatment for KD. The dataset contains detailed information on testing, diagnosis, medication, surgery, and any other clinical interventions with date of initiation. It also contains both suspected and confirmed disease names. Based on the information, we restricted study participants to only confirmed KD cases. We also confirmed the certainty of diagnosis by checking testing linked to disease name. Then we searched for all treatments for KD that were prescribed during the target period to identify the order and number of treatments. As treatment interventions were not labeled according to the order of initiation in the dataset, we identified 1st and 2nd line treatment according to the guidelines (2012) by identifying treatments related to confirmed KD during the initial admission. The identification was based on available data such as prescribed medicines with date of initiation and linked disease name. Then we organized the identified treatment lines in chronological order. The day on which additional treatment for refractory KD was initiated was regarded as the index date, based on the guidelines (2012) (i.e. the date on which 3rd line treatment for refractory KD was initiated when 1st line treatment included IVIG only or the date on which 2nd line treatment was initiated when 1st line treatment included combination therapy with IVIG and steroids) [22]. Although new guidelines for the medical treatment of acute-stage KD in Japan were published in October 2020 [23], the guidelines (2012) were used given that the study participants received treatment prior to publication of the new guidelines. The study participants were followed up from the index date until death, loss to follow-up in *TheBD*, or the end of the observation period (Fig. 1).

Exposure of interest

The main exposure of interest was receipt of IFX as additional treatment for KD that had been considered refractory to initial treatment. There is no biosimilar of IFX available in Japan.

Participants who received IFX at any time after the index date were allocated to the IFX group irrespective of other additional therapies. Participants who did not receive IFX as an additional treatment were allocated to the non-IFX group. Additional treatments other than IFX included IVIG, steroids, ulinastatin, immunosuppressants, and plasma exchange [22].

Measurement of effectiveness

The primary endpoint was cost-effectiveness, defined as the ratio of the number of admissions due to KD-related events to the total medical expenses during the same period (times/10,000 USD). Both the number of admissions and total medical expenses were converted to annual amounts after counting the totals for the full observation period, as this period varied across study participants. The time horizon was set as 1 year because this is the recommended minimum duration of follow-up for KD irrespective of cardiovascular complications [24], and most participants had records available 1 year from the index date.

Admission due to KD-related events was defined as initial admission for treatment in the acute phase or readmission due to recurrent KD or cardiovascular complications during the observation period. Medical expenses were defined as all inpatient, outpatient, and laboratory expenses during the same observation period. All services related to the management of KD or KD-related cardiovascular complications were covered, including testing/diagnosis, pharmacotherapy, treatment/surgery, hospitalized recuperation, rehabilitation, outpatient treatment.

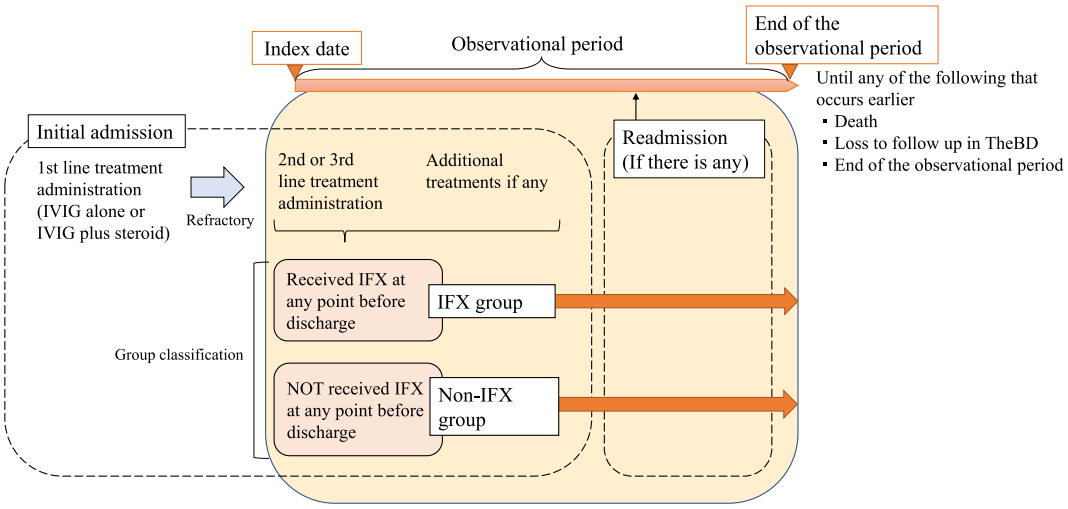

Fig. 1. Study timeline.
IFX, infliximab; IVIG, intravenous immunoglobulin; TheBD, The Tokyo University Health Economy Big Data.

The medical cost was converted from Japanese yen to US dollars using a mean rate of 112.23 yen per one US dollar, which was the exchange rate in 2017. We did not apply the discount rate but instead used the medical cost in 2017, when most study participants received treatment.

The secondary endpoint was the incidence of cardiovascular complications during the total observation period. Cardiovascular complications were defined as coronary artery complications or any other cardiovascular complications (e.g. ischemic heart disease, valvular abnormalities, arrhythmias, and cardiac or respiratory dysfunction) diagnosed after the onset of KD.

Analytical methods

Patient background characteristics were compared between the treatment groups. Student's *t*-tests or Wilcoxon rank-sum tests and chi-square tests were used for continuous and categorical variables, as appropriate. Primary and secondary outcomes were summarized and compared between the two treatment groups using a Wilcoxon rank-sum test with a significance level of 5%. All analyses were performed using Stata/MP 16.0 (StataCorp, College Station, TX, USA).

Propensity-score matching

For sensitivity analysis, propensity-score (PS) matching was performed by adjusting for differences in background characteristics between the two groups because there was a significant difference in the use of steroids during initial treatment. The significance level was set to 5%, and all tests were two-tailed. PS matching was performed using sex, age, incomplete KD, liver dysfunction at initial admission, dehydration at initial admission, use of steroids during initial IVIG treatment, number of IVIG treatments at the initial admission, and the year of the initial admission. These variables were selected to control for the severity of KD and risk factors for coronary artery complications. Previous studies have reported that male sex [25], age ≤ 12 months [25,26], resistance to initial IVIG [27,28], and delay in diagnosis [29] are risk factors for severe KD. However, we could not consider delays in diagnosis or biomarkers [30] in the propensity score because information regarding symptom onset and the results of laboratory tests are not recorded in *TheBD*. Instead, we considered liver dysfunction and dehydration at initial admission as proxies for disease severity. Incomplete KD was determined according to the registered disease name in *TheBD*. We could not verify the diagnosis of incomplete KD, as the database does not contain information regarding symptoms.

Sub-group analysis

We also performed a sub-group analysis to compare the characteristics and incidence of cardiovascular complications between those who received IFX as 2nd or 3rd line treatment [22] and those who received IFX later. This analysis did not involve statistical tests due to the limited sample size.

Ethical approval and informed consent

This medical economics study, which involved the use of big data, was given comprehensive approval in March 2019 by the Institutional Review Board of the University of Tokyo Hospital (screening no: 2018167NI). As we used database records for analysis, the need for informed consent was waived (opt-out format).

Statement of patient and public involvement

Neither the patients nor the public were involved in the design, conduct, reporting, or dissemination of our research.

Results

Among 7 million patients registered in *TheBD*, 1267 KD patients met eligibility criteria for the current study. This was close to the number of expected cases of KD based on the incidence rate reported in the nationwide survey of KD in Japan (313.4 per 100,000 per year among children from 0 to 4 years of age on average in 2012–2018) [1]. IFX was used in 26 patients with refractory KD (Fig. 2). One patient was excluded from the IFX group and allocated to the non-IFX group since he had received IFX at the time of recurrence long after the initial treatment. The non-IFX group included 206 patients.

Table 1 shows the background characteristics of the study participants according to treatment group. The proportion of men, mean age, and proportion of incomplete KD were comparable between the IFX and non-IFX groups. The frequency of steroid use during initial IVIG treatment was higher in the non-IFX group than in the IFX group (70.4% vs. 32.0%, $p < 0.001$). However, this frequency became comparable between the two groups after PS matching (32.0% vs. 32.0%) (Online Table 2, Online Fig. 1).

The median follow-up periods were 366 days [302, 602] in the IFX group and 467 days [347, 844] in the non-IFX group (Table 2), respectively. The numbers of admissions per annum were 1.21 [0.97, 2.09]

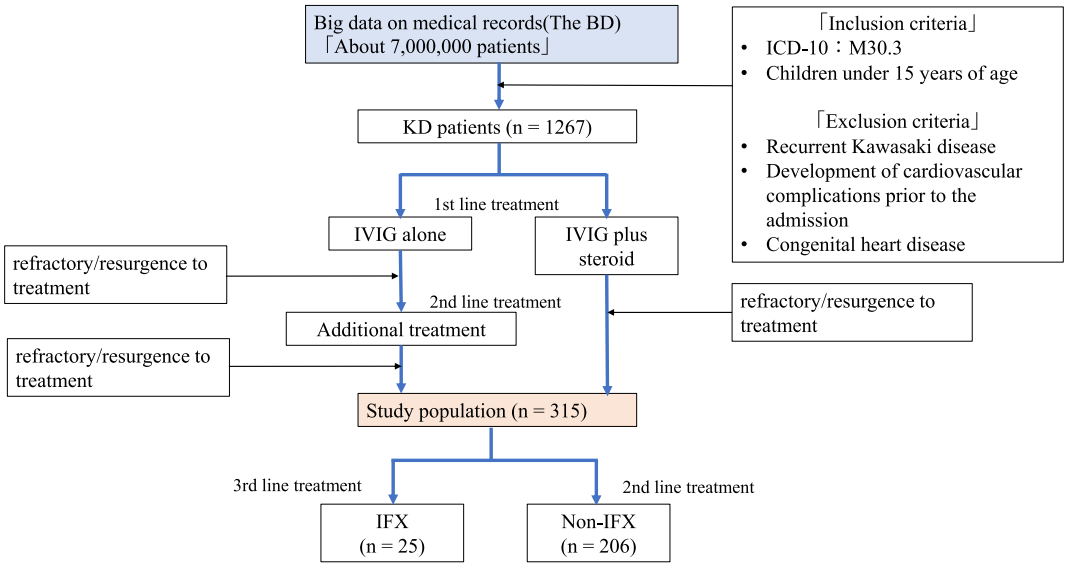

Fig. 2. Study participants. *One patient was excluded from the IFX group and allocated to the non-IFX group since he had received IFX at the time of recurrence long after the initial treatment.
IFX, infliximab; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; TheBD, The Tokyo University Health Economy Big Data.

and 1.65 [0.82, 2.31] for the IFX and non-IFX groups ($p = 0.645$), respectively. The total medical cost per annum was 10,939 USD [8321, 22,950] in the IFX group and 10,656 USD [6445, 21,549] in the non-IFX group ($p = 0.468$). The numbers of admissions per medical cost (time/10^4 USD) were 1.04 [0.86, 1.34] and 1.42 [0.99, 1.83] in the IFX and non-IFX groups ($p = 0.008$), respectively. In the PS-matched analysis, the respective numbers of admissions per medical cost (time/10^4 USD) for the IFX and non-IFX groups were 1.04 [0.86, 1.34] and 1.38 [1.03, 1.79] ($p = 0.006$).

During the full observation period, the frequency of cardiovascular and coronary artery complications was lower in the IFX group than in the non-IFX group (Table 3). However, this difference was not statistically significant.

Table 4 compares the background characteristics and outcome measures between patients who received IFX as 2nd or 3rd line treatment [or earlier (i.e. early treatment group)] and patients who received IFX later (later treatment group). Seven patients received IFX after 3 and more treatments with alternative medications. The number of days to the initiation of IFX in the early and late treatment groups was 4.6 ± 2.3 and 8.6 ± 5.3, respectively. Medical costs and the incidence of cardiovascular complications tended to be lower in the early treatment group than in the later treatment group; however, statistical analysis of this difference was not possible given the limited number of patients.

Table 1
Participant characteristics according to treatment group (N = 231).

Variables	IFX (n = 25)	Non-IFX (n = 206)	*p*-Value[a]
Baseline			
Sex			0.917
Male	16 (64.0)	134 (65.1)	
Female	9 (36.0)	72 (35.0)	
Age at onset (year)	3.0 [1.6]	2.5 [1.9]	0.213
Incomplete KD	1 (4.0)	11 (5.3)	0.776
Use of steroids during initial IVIG treatment	8 (32.0)	145 (70.4)	<0.001
Number of IVIG treatments at the first admission	2.2 [0.7]	2.5 [0.8]	0.186

Numbers are presented as n (%), mean [standard deviation].
IFX, infliximab; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.
[a] The Wilcoxon rank-sum test was applied.

Discussion

The present findings indicated that use of IFX for KD refractory to initial treatment may be more cost-effective than other treatment options. After PS matching, improvements in outcomes (numbers of admissions) were observed, and medical costs were slightly lower in the IFX group than in the non-IFX group. Consequently, the position was close to "dominant" in the cost-effectiveness plane, and the performance was considered excellent [31,32]. This means that expanded use of IFX for KD refractory to intimal treatment may reduce both disease and economic burden.

A cost-effectiveness analysis generally compares the costs associated with drug therapy (or full practice) with the clinical outcome (or safety) of the intervention [33]. Therefore, our analysis was slightly unusual in that we compared the cumulative number of admissions (events during the observation period) per cumulative cost of public health insurance between patients who received IFX and those who did not. This was because it was difficult to perform statistical analyses due to the limited number of patients with cardiovascular complications. However, as most readmissions occur due to the existence of cardiovascular complications, we considered the number of admissions a good surrogate for health outcomes. Although the difference was not significant, the incidence of cardiovascular complications tended to be lower in the IFX group than in the non-IFX group. This tendency may be reflected in the number of admissions, which was significantly lower in the IFX group than in the non-IFX group.

We aimed to capture the cost-effectiveness of treatment during the overall period from the standpoint of a public insurer with the wide perspective including patients with various backgrounds and severity of complications in different health facilities. We consider that choice of initial treatment can influence long-term health outcomes through severity of complications. Therefore, we have adjusted for surrogates of risk factors for coronary artery complications such as use of steroid as the combination therapy for the 1st line treatment. However, the dataset did not contain data on size of the coronary artery complication or other relevant data on severity. The lack of information on the severity of complications was a limitation of this study. Nonetheless, even if available, ability of the clinical information of severity such as z-score to adjust the variation in the cost-effectiveness may be limited because of measurement errors due to variations among examiners. It was

Table 2
Comparison of the number of admissions, medical costs, and cost-effectiveness.

	Unmatched			PS matched		
	IFX (N = 25)	Non-IFX (N = 206)		IFX (N = 25)	Non-IFX (N = 100)	
Before annual conversion	Median [Q2, Q3]	Median [Q2, Q3]	*p*-Value[a]			
Follow-up duration (days)	366 [302, 602]	467 [347, 844]	0.166	–	–	–
Number of admissions	1.56 [1.0, 2.0]	2.19 [1.0, 2.0]	0.007	–	–	–
Total medical cost (USD)	15,574.2 [10,904.0, 18,988.9]	19,420.1 [9699.8, 20,880.2]	0.842	–	–	–

	Unmatched			PS matched		
	IFX (N = 25)	Non-IFX (N = 206)		IFX (N = 25)	Non-IFX (N = 100)	
After annual conversion	Median [Q2, Q3]	Median [Q2, Q3]	*p*-Value[a]	Median [Q2, Q3]	Median [Q2, Q3]	*p*-Value[a]
Number of admissions (per annum)	1.21 [0.97, 2.09]	1.65 [0.82, 2.31]	0.645	1.21 [0.97, 2.09]	1.79 [0.86, 3.25]	0.319
Total medical cost (USD per annum)	10,939 [8321, 22,950]	10,656 [6445, 21,549]	0.468	10,939 [8321, 22,950]	11,791 [7433, 26,209]	0.941
Number of admissions per medical cost (time/10^4 USD per annum)	1.04 [0.86, 1.34]	1.42 [0.99, 1.83]	0.008	1.04 [0.86, 1.34]	1.38 [1.03, 1.79]	0.006

IFX, infliximab; PS, propensity score; SD, standard deviation; USD, United States dollars.
[a] The Wilcoxon rank-sum test was applied.

reported that there is heterogeneity in z-score calculation especially when coronary artery dimensions vary [34]. Further study will be needed to consider the severity of complications in calculation of cost-effectiveness using the standardized measurement methods.

Cumulative medical costs, the element of cost-effectiveness, are reported to be skewed to the severe cardiovascular lesions [35,36]. Although the medical fee system does not change the unit price based on category of complications of KD, we also see the skewness in medical costs among patients with coronary artery complications in this study, reflecting a displacement in consumption of medical resources. Thus, we consider that severity of complications is reflected in the cumulative medical cost of the medical service bills produced based on the content (pharmacotherapy, inpatient treatment) and density (number of times, number of days) of medical treatments. Overall, we consider that the severity of complications is an important factor for both health outcomes and cumulative medical cost, but its influence on cost-effectiveness is limited.

Additionally, the present preliminary study indicates that earlier initiation of IFX (as 2nd or 3rd line treatment) may reduce the risk of cardiovascular complications as well as medical costs in patients with initially refractory KD. Notably, patients who receive IFX after several other treatments may exhibit severe disease and have a high risk of developing cardiovascular complications [12]. However, it was difficult to evaluate the potential reverse causation, as the chronological order of IFX initiation and the onset of cardiovascular complications was not clear based on the medical big data used in this study. Further studies of databases containing detailed clinical information and those with larger sample sizes are required to verify the effects of early initiation of IFX treatment on health outcomes in patients with KD refractory to initial treatment.

The strength of this study is that *TheBD* contains representative data for a large number of patients and hospitals across Japan, meaning that the results can be generalized to the Japanese population. Secondly, *TheBD* data reflect the real-world situation of KD treatment in Japan. Analyses of real-world data are most suitable for cost-effectiveness analysis. However, this study was not without limitations. First, the sample size, especially in the IFX group, was not large enough to perform statistical comparisons of the occurrence of cardiovascular complications. As IFX is a relatively new medicine that has only been covered by public health insurance since 2015, its use in patients with KD remains limited to some hospitals despite a recent increase [12,13]. Second, several clinical variables are not included in the database, such as fever, symptoms, biomarker levels, and size of coronary artery aneurysm. The presence of fever is clinically important when attempting to confirm refractory cases [22,23]; however, in this study, cases in which additional treatments were performed were regarded as refractory instead. This assumption is reasonable, as patients can usually receive necessary treatment in the Japanese medical system. Symptoms

Table 3
Comparison of outcome measures according to treatment group (N = 231).

Variables	IFX (n = 25)	Non-IFX (n = 206)	*p*-Value[a]
Additional treatment during the first admission			
Plasma exchange	2 (8.0)	20 (9.7)	0.783
Immunosuppressant	1 (4.0)	22 (10.7)	0.292
At the end of observation period			
Cardiovascular complications	6 (24.0)	70 (34.0)	0.316
Coronary artery complications	3 (12.0)	48 (23.3)	0.198

Numbers are presented as n (%).
IFX, infliximab.
[a] The Wilcoxon rank-sum test was applied.

Table 4
Comparison of characteristics and outcome measures with respect to timing of IFX initiation (N = 25).

Variable	Early (N = 18)	Late (N = 7)
Baseline		
Sex		
Male	13 (72.2)	3 (42.9)
Female	5 (27.8)	4 (57.1)
Age (years)	3.1 [1.7]	2.9 [1.2]
At the end of the observation period		
Days to IFX initiation	4.6 [2.3]	8.6 [5.3]
Total medical cost (USD)	1490 [754]	1730 [658]
Cardiovascular complications	3 (16.7)	2 (28.6)
Coronary artery complications	1 (5.6)	2 (28.6)

Numbers are presented as n (%) or mean [standard deviation] values.
IFX, infliximab; USD, United States dollars.

are also important for confirming cases of incomplete KD. We considered patients to have incomplete KD if the disease name "incomplete KD" was registered in the database, although the frequency of incomplete KD may have been underestimated if not all cases of incomplete KD were registered. Furthermore, measurements of biomarker levels are necessary to control for disease severity [37], and the lack of these data may have affected the comparability of the two groups. Nonetheless, we attempted to make the two groups homogeneous by applying PS matching using available data such as sex, age, type of KD, existence of liver dysfunction and dehydration at admission, and the use of steroids during initial IVIG treatment. Notably, the use of steroids during initial IVIG treatment has been associated with disease severity, and such treatment is recommended for patients with high risk scores [9]. Third, only the months of diagnosis and treatment were available for some participants. Without the exact date of diagnosis and treatment initiation, it was difficult to determine whether cardiovascular complications preceded the initiation of treatment. We excluded patients diagnosed with cardiovascular/coronary artery complications before the date of admission only when data were available. Patients who received IFX at a later time may have developed complications before treatment, which may have resulted in underestimation of the effectiveness of IFX. Also, we had to assume the timing of additional treatment based on available data such as name and dose of medicines, timing of testing, and diagnosis for some patients who did not have date of treatment initiation. This uncertainty may have led to bias to some extent. Fourth, our cost-effectiveness analysis considered only limited events such as the number of admissions. Coronary artery and cardiovascular complications, which are clinically important outcomes, were not considered owing to the limited number of events. Finally, the present study did not consider quality of life (QoL), which is an important health outcome in cost-effectiveness analysis [38]. QoL information was not available in the dataset, and QoL has not been measured in Japanese patients with KD. Further research is required to evaluate the incremental cost-effectiveness ratio (ICER) using QoL data. Despite these limitations, our study offers important implications for clinical practice and future research.

Conclusion

The results of the current study indicate that IFX may be more cost-effective than other treatment options in patients with KD refractory to initial treatment with IVIG. Our findings may aid clinicians in selecting additional treatment strategies in this population. Although the frequency of cardiovascular/coronary artery complications was lower in the IFX group and those in whom IFX treatment was initiated early, statistical analysis of these differences was not possible due to the small number of patients. Further studies with the larger number of participants are required to confirm the differences in health outcomes between patients treated with and without IFX and between early and later initiation of IFX. Analyses of the ICER that consider patient QoL also remain necessary.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.03.005.

Funding

This work was supported by Ministry of Health, Labour, and Welfare of Japan (19FC2001). The funding agency was not involved in the study design, data analysis, or interpretation of the present findings.

CRediT authorship contribution statement

SH conceptualized the study. TT and SH designed the study and analysis strategy. SH performed data analysis, and TT and SH interpreted the data. TT and SH drafted the manuscript and approved the final version. TT and SH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

Owing to the sensitive nature of the data collected for this study, data supporting the findings of the study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors have nothing to declare.

Acknowledgments

This work was reported at the 13th International Kawasaki Disease Symposium held on October 29–31, 2021.

References

[1] Research group on Kawasaki Disease National Survey. National survey on Kawasaki disease treatment in Japan. Tochigi: Japan Kawasaki Disease Research Center; 2019. https://www.jichi.ac.jp/dph/wp-dph/wp-content/uploads/2019/09/1bb34be7b6c9f852c1df45cc2ac4152c-1.pdf.

[2] Burns JC, Shike H, Gordon JB, Malhotra A, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. J Am Coll Cardiol 1996;28:253–7. https://doi.org/10.1016/0735-1097(96)00099-x.

[3] Suda K, Iemura M, Nishiono H, Teramachi Y, Koteda Y, Kishimoto S, et al. Long-term pr. ognosis of patients with Kawasaki disease complicated by giant corona. ry aneurysms: a single-institution experience. Circulation 2011;123:1836–42. https://doi.org/10.1161/CIRCULATIONAHA.110.978213. .

[4] Furusho K, Nakano H, Shinomiya K, Tamura T, Manabe Y, Kawarano M, et al. High-d. ose intravenous gammaglobulin for Kawasa. ki disease. Lancet 1984;324:1055–8. https://doi.org/10.1016/S0140-6736(84)91504-6.

[5] Newburger JW, Takahashi M, Burns JC, Beiser AS, Chung KJ, Duffy CE, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. . N Engl J Med 1986;315:341–7. https://doi.org/10.1056/NEJM198608073150601.

[6] Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. . N Engl J Med 1991;324:1633–9. https://doi.org/10.1056/NEJM199106063242305.

[7] Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. J Pediatr 199. 7;131:888–93. https://doi.org/10.1016/s0022-3476(97)70038-6.

[8] Oates-Whitehead RM, Baumer JH, Haines L, Love S, Maconochie IK, Gupta A, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. Cochrane Database Syst Rev 2003 2003;4:CD004000. https://doi.org/10.1002/14651858.CD004000.

[9] Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, et al. Efficac. y of immunoglobulin plus. prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. Lancet 2012;379:1613–20. https://doi.org/10.1016/S0140-6736(11)61930-2.

[10] Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatmen. t for immune globulin-resistant Kawasaki disease: a c. omparative study of additional immune globulin and steroid pulse therapy. Pediatr Int 2001;43:211–7. https://doi.org/10.1046/j.1442-200x.2001.01373.x.

[11] Burns JC, Best BM, Mejias A, Mahony L, Fixler DE, Jafri HS, et al. . Infliximab treatment of intravenous immunoglobulin–resistant Kawasaki disease. J Pediatr 2008;153:833–8. https://doi.org/10.1016/j.jpeds.2008.06.011.

[12] Masuda H, Kobayashi T, Hachiya A, Nakashima Y, Shimizu H, Nozawa T, et al. Infliximab fo. r the treatment of refractory Kawasaki disease: a nationwide survey in Japan. J Pediatr 2018;195:115–120.e3. https://doi.org/10.1016/j.jpeds.2017.10.013.

[13] Miura M, Kobayashi T, Igarashi T, Hamada H, Iwata N, Sasaki Y, et al. Real-world safety. and effectiveness of infliximab in pediatric patien. ts with acute Kawasaki disease: a postmarketing surveillance in Japan (SAKURA Study). Pediatr Infect Dis J 2020;39:41–7. https://doi.org/10.1097/INF.0000000000002503.

[14] Miura M, Tamame T, Naganuma T, Chinen S, Matsuoka M, Ohki H. Steroid pulse therapy for Kawasaki disease unresponsive to additional immunoglobulin therapy. Paediatr Child Healt h 2011;16:479–84. https://doi.org/10.1093/pch/16.8.479.

[15] Suzuki H, Terai M, Hamada H, Honda T, Suenaga T, Takeuchi T, et al. Cyclosporin A treatment for Kawasaki disease refractory to initial and additional intravenous immunoglobulin. Pediatr Infect Dis J 2011;30:871–6. https://doi.org/10.1097/INF.0b013e318220c3cf.

[16] Imagawa T, Mori M, Miyamae T, Ito S, Nakamura T, Yasui K, et al. Plasma exchange for refractory Kawasaki disease. . Eur J Pediatr 2004;163:263–4. https://doi.org/10.1007/s00431-003-1267-y.

[17] Hokosaki T, Mori M, Nishizawa T, Nakamura T, Imagawa T, Iwamoto M, et al. Long-term efficacy of plasma exchange treatment for refractory Kawasaki disease. Pediatr Int 2012;54:99–103. https://doi.org/10.1111/j.1442-200X.2011.03487.x.
[18] Crayne CB, Mitchell C, Beukelman T. Comparison of second-line . therapy in IVIg-refractory Kawasaki disease:. a systematic review. Pediatr Rheumatol Online J 2019; 17:77. https://doi.org/10.1186/s12969-019-0380-z.
[19] Johnson SC, Williams DC, Brinton D, Chew M, Simpson A, Andrews AL. A cost comparison of infliximab versus intravenous immunoglobulin for refractory Kawasaki disease treatment. Hosp Pediatr 2021;11:88–93. https://doi.org/10.1542/hpeds.2020-0188.
[20] Takura T, Yokoi H, Tanaka N, Matsumoto N, Yoshida E, Nakata T, et al. Health economics-based verification of function. al myocardial ischemia evaluation of stable coronary artery disease in Japan: a long-term longitudinal study using propensity score matching. J Nucl Cardiol 2021. https://doi.org/10.1007/s12350-020-02502-9.
[21] The University of Tokyo Japan. The Tokyo university health economy big data. http://plaza.umin.ac.jp/hehp/pdf/thebd.pdf.
[22] 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 med. ical 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. https://doi.org/10.1111/ped.12317.
[23] Miura M, Ayusawa M, Fukazawa R, Hamada H, Ikeda S, Ito S, et al. Guidelines for Medical Treatment of Acute Kawasaki Disease (2020 Revised Version). J Pediatr Cardiol Card Surg 2021;5:41–73. https://doi.org/10.24509/jpccs.0501G1.
[24] Japanese Circulation Society (JCS) Joint Working Group. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS2013). Circ J 2014; 78:2521–62. https://doi.org/10.1253/circj.CJ-66-0096.
[25] Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, Aoyama Y, et al. Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. J Epidemiol 2012;22:216–21. https://doi.org/10.2188/jea.je20110126.
[26] Song D, Yeo Y, Ha K, Jang G, Lee J, Lee K, et al. Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. Eur J Pediatr 2009;168: 1315–21. https://doi.org/10.1007/s00431-009-0925-0.
[27] Beiser AS, Takahashi M, Baker AL, Sundel RP, Newburger JW. A predictive instrument for coronary artery aneurysms in Kawasaki disease. US Multicenter Kawasaki Disease Study Group. Am J Cardiol 1998;81:1116–20. https://doi.org/10.1016/s0002-9149(98)00116-7.
[28] Koren G, Lavi S, Rose V, Rowe R. Kawasaki disease: review of risk factors for coronary aneurysms. J Pediatr 1986;108:388–92. https://doi.org/10.1016/s0022-3476(86)80878-2.
[29] Qiu H, He Y, Rong X, Ren Y, Pan L, Chu M, et al. Delayed intravenous immunoglobulin treatment increased the risk of coronary artery lesions in children with Kawasaki disease at different status. Postgrad Med 2018;130:442–7. https://doi.org/10.1080/00325481.2018.1468712.
[30] Kong WX, Ma FY, Fu SL, Wang W, Xie CH, Zhang YY, et al. Biomarkers of intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. World J Pediatr 2019;15:168–75. https://doi.org/10.1007/s12519-019-00234-6.
[31] Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making 1990;10:212–4. https://doi.org/10.1177/0272989X9001000308.
[32] Cohen DJ, Reynolds MR. Interpreting the results of cost-effectiveness studies. J Am Coll Cardiol 2008;52:2119. https://doi.org/10.1016/J.JACC.2008.09.018.
[33] Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296:716–21. https://doi.org/10.1056/NEJM197703312961304.
[34] Liu HH, Qiu Z, Fan GZ, Jiang Q, Li RX, Chen WX, et al. Assessment of coronary artery abnormalities and variability of Z-score calculation in the acute episode of Kawasaki disease—a retrospective study from China. Eur J Clin Invest 2021;51:e13409. https://doi.org/10.1111/ECI.13409.
[35] Takura T, Tachibana K, Isshiki T, Sumitsuji S, Kuroda T, Mizote I, et al. Preliminary report on a cost-utility analysis of revascularization by percutaneous coronary intervention for ischemic heart disease. Cardiovasc Interv Ther 2017;32:127–36. https://doi.org/10.1007/s12928-016-0401-5.
[36] Lim HS, Shaw S, Carter AW, Jayawardana S, Mossialos E, Mehra MR. A clinical and cost-effectiveness analysis of the HeartMate 3 left ventricular assist device for transplant-ineligible patients: a United Kingdom perspective. J Heart Lung Transplant 2022;41:174–86. https://doi.org/10.1016/J.HEALUN.2021.11.014.
[37] Kobayashi T, Inoue Y, Otani T, Morikawa A, Kobayashi T, Takeuchi K, et al. Risk stratification in the decision to include prednisolone with intravenous immunoglobulin in primary therapy of Kawasaki disease. Pediatr Infect Dis J 2009;28:498–502. https://doi.org/10.1097/INF.0B013E3181950B64.
[38] Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures. . Circulation 2014;129:2329–45. https://doi.org/10.1161/CIR.0000000000000042.