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Useful predictors of Kawasaki disease without complications before initial acute-phase treatment

Toshimasa Nakada *

Department of Pediatrics, Aomori Prefectural Central Hospital, 030-8553 Higashi- tukurimiti 2-1-1, Aomori City, Aomori Prefecture, Japan.

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Abstract

Kawasaki disease (KD) is an acute febrile systemic vasculitis that primarily affects children younger than 5 years, with coronary artery lesions (CALs) as its severe complications. Intravenous immunoglobulin (IVIG) therapy resistance has been implicated in CAL development, and its known predictors are as follows: Egami score, Kobayashi score, C-reactive protein (CRP), albumin, CRP-to-albumin ratio, and neutrophil-to-lymphocyte ratio (NLR). However, the most useful predictor for IVIG resistance in patients with KD without complications before initial acute-phase treatment remains unclear. Therefore, this study aimed to determine the most useful predictor for IVIG resistance in such patients. This retrospective study included data from 202 patients with KD who underwent acute-phase treatment from January 2009 to March 2021. Among 46 IVIG-resistant patients, 22 patients required rescue therapy (rescued patients), while the remaining 24 received no rescue therapy for resistance and had no CALs. Among the 6 indices, NLR had the highest sensitivity and specificity for the detection of all IVIG-resistant patients and rescued patients (0.724 and 0.728, respectively), and logistic regression analysis showed that the NLR was the sole independent predictor both for the IVIG-resistant patients and for the rescued patients ($P < 0.001$ and $= 0.002$, Odds ratio = 5.797 and 5.814, 95% confidence interval = 2.687–12.504 and 1.954–17.299, respectively). NLR was the useful predictor for all IVIG-resistant patients and rescued patients among those with KD without complications before initial acute-phase treatment.

Keywords: Kawasaki disease; Neutrophil-to-lymphocyte ratio; Predictors; Intravenous immunoglobulin therapy resistance; Coronary artery lesions

1. Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis that primarily affects children younger than 5 years [1], and coronary artery lesions (CALs) can arise as severe complications [2]. Appropriate risk stratification and acute-phase treatment are important for preventing of severe CALs [3–5]. Studies have shown that complications such as CALs and status epilepticus before initial treatment suggest severe KD [6, 7]. The findings of the nationwide epidemiological survey in Japan showed that a 3.4% prevalence of patients with CALs before initial treatment [8]. Moreover, a recent clinical report showed that the rate of patients with CALs/status epilepticus before initial treatment was 2.3% [9]. Therefore, majority of patients with KD have no complications before initial acute-phase treatment. However, risk stratification among those patients has not been established.

Intravenous immunoglobulin (IVIG) therapy resistance during the acute-phase of KD has been implicated in CAL development [10] and has been identified in patients when the fever either persists or reappears 24 h after the initial KD treatment [11].

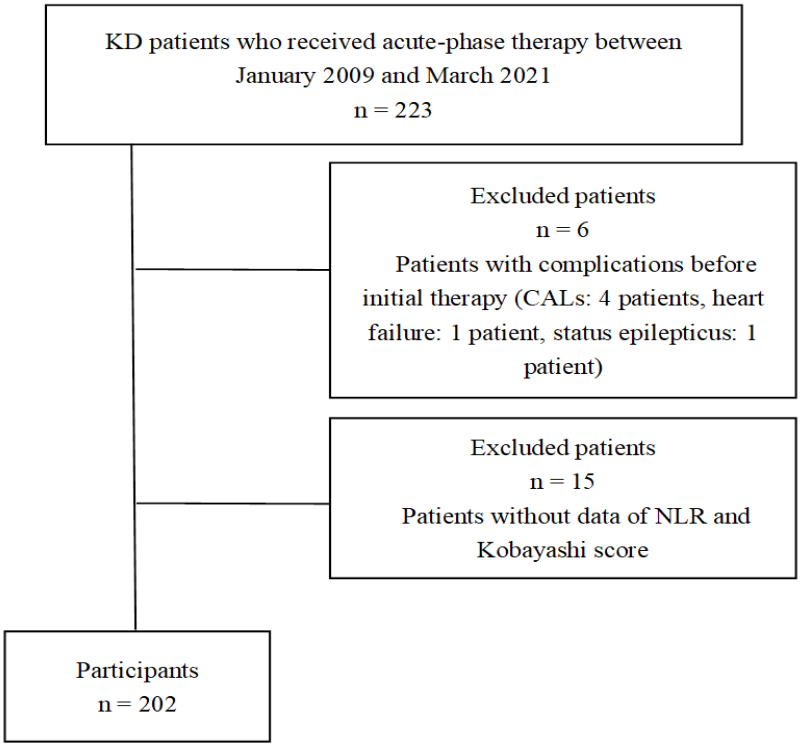
* Corresponding author: Toshimasa Nakada
Department of Pediatrics, Aomori Prefectural Central Hospital 030-8553 Higashi- tukurimiti 2-1-1, Aomori City, Aomori Prefecture, Japan.

Egami score, Kobayashi score, C-reactive protein (CRP) levels, albumin levels, CRP-to-albumin ratio (CAR), and neutrophil-to-lymphocyte ratio (NLR) have all been reported as predictors for IVIG resistance [10, 12–17]. However, the most useful predictor for IVIG resistance in patients with KD without complications before initial acute-phase treatment remains unclear. Therefore, this retrospective study was conducted to elucidate the most useful predictor for IVIG resistance in those patients.

2. Material and methods

2.1. Participants and Methods

This retrospective study included data from 202 patients with KD who underwent acute-phase treatment from January 2009 to March 2021. First-time KD patients were included. A total of 6 patients with complications before initial therapy (CALs: 4, heart failure: 1, status epilepticus: 1) and 15 patients with unknown NLR and Kobayashi score were excluded (Figure 1).



KD: Kawasaki disease, CALs: coronary artery lesions, NLR: neutrophil-to-lymphocyte ratio

Figure 1 Study Profile

The total study population (202 patients) was divided into 46 IVIG-resistant patients and 156 non-resistant patients. A total of 22 IVIG-resistant patients who required rescue therapy for resistance were defined as the rescued patients. KD was diagnosed based on the criteria (Japanese, 5th edition) mentioned in the diagnostic guidelines for KD until August 2019 and in the revised criteria (Japanese, 6th edition), which was adopted in September 2019 [2, 18]. Egami score, Kobayashi score, CRP levels, albumin levels, CAR, and NLR before initial treatment were studied.

2.2. Initial Therapy

During the study period, a single IVIG infusion of 2 g/kg/dose was given as initial therapy starting on day 5 of the illness, whenever possible [9]. Patients without inflammation or complications at presentation received acute-phase therapy without IVIG [9]. Between January 2009 and November 2017, anti-inflammatory drugs (aspirin or flurbiprofen) were initiated within 24 h after the initial IVIG infusion ended [19]. Aspirin and flurbiprofen were started at 30 and 3–5 mg/kg/day, respectively, then decreased to 5–10 and 3 mg/kg/day, respectively, once the patient became afebrile [19]. Each attending physician chose aspirin or flurbiprofen after considering the patient's liver function and the risk of Reye syndrome during influenza season. After December 2017, low-dose aspirin (5 mg/kg/day) was started on days 8–10 of illness after completion of IVIG infusion, including the second course of therapy [9].

2.3. Rescue Therapy

The decision to use rescue therapies in resistant patients was made 48−72 h after completing the initial IVIG infusion. Physicians made this decision using comprehensive clinical parameters, including body temperature, major KD symptoms, general condition, and laboratory data [9]. The second course of therapy comprised rescue IVIG infusion at 2 g/kg/dose, and the third course comprised of an ulinastatin infusion, third course of IVIG therapy, or plasma exchange [9].

2.4. Diagnosis of CAL

Echocardiography was used to diagnose CALs based on the Japanese criteria reported by Kobayashi et al [10]. These were diagnosed if any examination showed an internal lumen diameter of ≥ 3 mm in a patient younger than 5 years or a diameter of ≥ 4 mm in a patient older than 5 years if the internal diameter of a segment was at least 1.5 times that of an adjacent segment, or if the lumen appeared irregular. Transient CAL was defined as the disappearance of a CAL within 30 days of the illness.

2.5. Statistical Analysis

Statistical analyses were conducted using Stat Flex Version 6 for Windows (Artech Co.,Ltd., Osaka, Japan). Chi-square, Fisher exact, and Mann–Whitney U tests were used as appropriate, with sample size considerations. Correlation analysis was performed to determine the significance of the relationships between laboratory indices. Receiver operating characteristic curves were used to determine the cut-off value of each parameter. Logistic regression analysis was used to determine independent predictor for IVIG-resistant patients and rescued patients. $P < 0.05$ was considered statistically significant.

3. Results

Statistically significant correlations were found between CRP and albumin levels, CRP levels and NLR, and albumin levels and NLR ($P < 0.001$) (Figure 2). The sensitivities of the Egami and Kobayashi scores for IVIG resistance were below 65% (Table 1).

Table 1 Egami and Kobayashi scores for intravenous immunoglobulin-resistant patients

Score	IVIG-resistant patients	Non-resistant patients
Egami ≥ 3	17	20
Egami ≤ 2	29	136
Kobayashi ≥ 5	15	9
Kobayashi ≤ 4	31	147

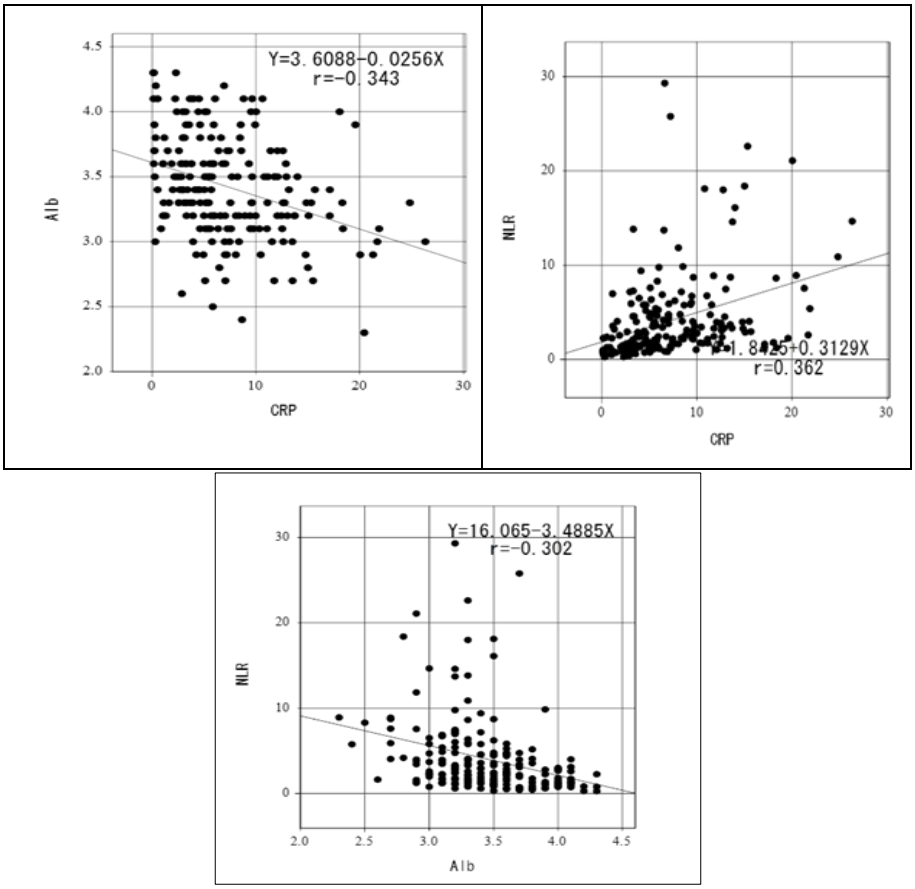
IVIG: intravenous immunoglobulin

Sensitivity of Egami score = 17/37 (46.0%). Specificity of Egami score = 136/165 (82.4%).

Sensitivity of Kobayashi score = 15/24 (62.5%). Specificity of Kobayashi score = 147/178 (82.6%).

Egami score, Kobayashi score, CRP levels, albumin levels, CAR, and NLR before initial treatment were significantly different between IVIG-resistant and non-resistant patients (Table 2). Moreover, those indices before initial treatment were significantly different between rescued and non-rescued patients (Table 3). The rate of CALs less than one month after KD onset in IVIG-resistant patients was significantly higher than that of non-resistant patients (Table 2). Moreover, the rates of CALs both less than one month and one month after KD onset in the rescued patients were significantly higher than those of non-rescued patients (Table 3). Aside from the 22 rescued patients, the other 24 IVIG-resistant patients received no rescue therapy for resistance and had no CALs. One patient with CAL in the non-rescue group was responsive to IVIG and had a transient CAL.

NLR had the highest sensitivity and specificity for the detection of IVIG-resistant patients and rescued patients compared with the other indicators (i.e., Egami score, Kobayashi score, CRP levels, albumin levels, and CAR) (Tables 4 and 5). Furthermore, logistic regression analysis showed that NLR was the sole independent predictor for both IVIG-resistant and rescued patients (Tables 6 and 7).



Correlations Between C-reactive protein (CRP) levels and albumin (Alb) levels,
CRP levels and neutrophil-to- lymphocyte ratio (NLR), and Alb levels and NLR were statistically significant (p<0.001)

Figure 2 Correlations among laboratory indices before initial treatment

Table 2 Comparison of clinical findings, treatments, and outcomes between intravenous immunoglobulin-resistant and non-resistant patients

Variables	IVIG resistant patients (n = 46)	Non-resistant patients (n = 156)	P-value
Male gender	24 (52.2%)	76 (48.7%)	0.680
Age at KD onset (months)	30.0 (21.0–51.0)	24.0 (12.0–44.5)	0.043
Incomplete KD	6 (13.0%)	32 (20.5%)	0.255
Egami score	2.0 (1.0–3.0)	1.0 (0.0–2.0)	< 0.001
Kobayashi score	3.0 (1.0–5.0)	1.0 (1.0–3.0)	< 0.001
CRP (mg/dL)	8.60 (5.66–12.93)	5.38 (2.95–9.46)	< 0.001
Albumin (g/dL)	3.20 (3.00–3.40)	3.50 (3.20–3.70) (n = 154)	< 0.001
CAR	2.62 (1.65–3.87)	1.57 (0.84–2.62) (n = 154)	< 0.001
NLR	5.21 (3.43–8.62)	2.22 (1.21–3.84)	< 0.001
Day of illness of evaluation	5.0 (5.0–6.0)	5.0 (5.0–6.0)	0.282
IVIG therapy	46 (100.0%)	139 (89.1%)	0.029

Start day of illness of initial IVIG therapy	5.0 (5.0–6.0)	5.0 (5.0–6.0) (n = 139)	0.114
Low-dose aspirin/ Medium-dose aspirin/ Flurbiprofen	14 (30.4%) 17 (37.0%) 15 (32.6%)	35 (22.4%) 76 (48.7%) 45 (28.8%)	0.266 0.160 0.624
CAL			
Less than one month after KD onset	3 (6.5%)	1 (0.6%)	0.038
One month after KD onset	2 (4.3%)	0 (0.0%)	0.051

Data are presented as n (%) or median (interquartile range); IVIG: intravenous immunoglobulin, KD: Kawasaki disease, CRP: C-reactive protein, CAR: C-reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio, CAL: coronary artery lesion; Incomplete KD: major signs of KD ≤ 4.

Table 3 Comparison of clinical findings, treatments, and outcomes between rescued and non-rescued patients

Variables	**Rescued patients (n = 22)**	**Non-rescued patients (n = 180)**	**P-value**
Male gender	9 (40.9%)	91 (50.6%)	0.393
Age at KD onset (months)	28.0 (21.0–60.0)	24.0 (13.0–45.5)	0.158
Incomplete KD	2 (9.1%)	36(20.0%)	0.264
Egami score	2.0 (1.0–4.0)	1.0 (0.0–2.0)	< 0.001
Kobayashi score	4.0 (2.0–6.0)	1.0 (1.0–3.0)	< 0.001
CRP (mg/dL)	9.59 (5.84–15.01)	5.58 (3.11–9.63)	0.002
Albumin (g/dL)	3.15 (2.80–3.30)	3.50 (3.20–3.70) (n = 178)	< 0.001
CAR	3.04 (2.04–5.36)	1.65 (0.91–2.79) (n = 178)	< 0.001
NLR	6.52 (4.02–8.73)	2.35 (1.26–4.42)	< 0.001
Day of illness of evaluation [mean +/– standard deviation]	5.0 (4.0–5.0) [4.86 +/– 0.77]	5.0 (5.0–6.0) [5.47 +/– 1.60]	0.040
IVIG therapy	22 (100.0%)	163 (90.6%)	0.226
Start day of illness of initial IVIG therapy [mean +/– standard deviation]	5.0 (5.0–5.0) [5.18 +/– 0.66]	5.0 (5.0–6.0) [5.69 +/– 1.33] (n = 163)	0.012
Low-dose aspirin/ Medium-dose aspirin/ Flurbiprofen	7 (31.8%) 7 (31.8%) 8 (36.4%)	42 (23.3%) 86 (47.8%) 52 (28.9%)	0.381 0.156 0.469
CAL			
Less than one month after KD onset	3 (13.6%)	1 (0.6%)	0.004
One month after KD onset	2 (9.1%)	0 (0.0%)	0.011

Data are presented as n (%) or median (interquartile range).; IVIG: intravenous immunoglobulin, KD: Kawasaki disease, CRP: C-reactive protein, CAR: C-reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio, CAL: coronary artery lesion; Incomplete KD: major signs of KD ≤ 4.

Table 4 Receiver operating characteristic curves analysis for the detection of IVIG-resistant patients

Variables	Cut-off value	Sensitivity=specificity	Area under curve
Egami score	1.08	0.671	0.703
Kobayashi score	1.49	0.643	0.704
CRP	6.59	0.596	0.668
Albumin	3.35	0.657	0.676
CAR	2.06	0.623	0.681
NLR	3.56	0.724	0.778

CRP: C-reactive protein, CAR: C-reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio.

Table 5 Receiver operating characteristic curves analysis for the detection of rescued patients

Variables	Cut-off value	Sensitivity=specificity	Area under curve
Egami score	1.37	0.711	0.796
Kobayashi score	2.08	0.717	0.807
CRP	7.03	0.606	0.700
Albumin	3.29	0.703	0.778
CAR	2.31	0.636	0.728
NLR	4.02	0.728	0.804

CRP: C-reactive protein, CAR: C-reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio.

Table 6 Logistic regression analysis for IVIG-resistant patients

Variables	P value	Odds ratio	95% confidence interval
Group 1			
Egami score	0.615	1.361	0.410–4.519
Kobayashi score	0.628	1.252	0.505–3.102
C- reactive protein	0.591	0.536	0.055–5.189
Albumin	0.033	0.402	0.175–0.927
CAR	0.453	2.438	0.238–25.001
NLR	< 0.001	5.168	2.343–11.401
Group 2			
NLR	< 0.001	5.797	2.687–12.504
Albumin	0.004	0.321	0.147–0.702

CAR: C- reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio

Table 7 Logistic regression analysis for rescued patients

Variables	P value	Odds ratio	95% confidence interval
Group 1			
Egami score	0.035	4.429	1.108–17.713
Kobayashi score	0.419	1.650	0.490–5.555
C- reactive protein	1.000	1.000	0.173–5.772
Albumin	0.053	0.329	0.107–1.012
CAR	0.952	1.056	0.177–6.319
NLR	0.016	4.351	1.309–14.461
Group 2			
NLR	0.002	5.814	1.954–17.299
Egami score	0.004	6.806	1.864–24.848

CAR: C- reactive protein-to-albumin ratio, NLR: neutrophil-to-lymphocyte ratio

4. Discussion

The key finding of this study is that the NLR had the highest sensitivity and specificity for the detection of IVIG-resistant and rescued patients compared with the Egami score, Kobayashi score, CRP levels, albumin levels, and CAR. Furthermore, logistic regression analysis showed that NLR was the sole independent predictor for both IVIG-resistant and rescued patients.

Physical immune system responses to systemic inflammation included marked neutrophilia and lymphocytopenia, and the NLR is a powerful biomarker of systemic inflammation [20]. Neutrophils are indicative of active non-specific inflammation, and lymphocytes represent the regulatory pathway of the immune system [21]. NLR may help reflect systemic inflammation and the immune system response in patients with KD [21]. Ha et al. have demonstrated that NLR can predict CAL development and IVIG resistance of KD [15]. Furthermore, our previous studies indicated the usefulness of NLR for the risk stratification of KD regarding IVIG resistance, CALs, and KD relapse [3, 5, 22, 23]. One study showed that laboratory values such as CRP, albumin, and neutrophil differential correlated with each other during the peak stage of systemic inflammation in KD [24]. In the present study, the correlations between the values of CRP and albumin, CRP and NLR, and albumin and NLR were also statistically significant ($P < 0.001$) (Figure 2), and logistic regression analysis showed that NLR was the sole independent predictor of both IVIG-resistant and rescued patients (Tables 6 and 7).

The sensitivities for IVIG resistance of the Egami and the Kobayashi score systems were below 65% (Table 1). This low sensitivity may be because those score systems did not include NLR [10, 12]. Because of the low sensitivity of those score systems, caution must be taken regarding overtreatment during clinical practice in the acute-phase of KD. In the studies which utilized the Kobayashi score system, the proportion of the patients predicted to be IVIG-resistant were 29.8%–27.6% of the acute-phase KD population [7, 10]. On the other hand, the proportion of the IVIG-resistant patients who received rescue therapies was 10.1% in the study, which was conducted without utilization of the Kobayashi/Egami score systems [9]. Moreover, a recent Japanese nationwide survey regarding patients with KD in 2015 and 2016 showed that the rates of rescue therapy and cardiac sequalae one month after onset were 21.8% and 2.3%, respectively [8]. In the study that was conducted without utilization of the Kobayashi/Egami score systems, those rates were 13.7% and 1.9%, respectively [9]. Several genetic studies have identified genes associated with KD and some of these genes can predict the course and coronary outcomes in the affected individuals [25]. However, the appropriate genetic tests are not yet available in clinical practice in the acute-phase of KD, in contrast to NLR, which is readily available. The cut-off values of NLR before initial therapy for high-risk patients regarding IVIG resistance and CAL were reported as 5.0 and 3.5, respectively [17, 21]. Those values were similar to the cut-off values of NLR for IVIG-resistant and rescued patients in the present study: 3.56 and 4.02, respectively (Tables 4 and 5).

One study indicated that CAR could serve as a novel predictive marker for IVIG resistance in KD [13]. However, another study showed that the value of CAR was not better than either CRP or albumin alone for initial IVIG resistance prediction [14]. The present study also indicated that CAR was not superior to either CRP or albumin alone (Tables 6 and 7). Our previous study regarding the predictive ability of CAR after initial IVIG therapy also showed that it was not superior to that of CRP alone [26]. The logistic regression analysis for the IVIG-resistant patients in the present study suggested that albumin alone may be superior to CAR for predicting IVIG resistance in KD patients without complications before initial acute-phase treatment (Table 6).

This study suggested the superior ability of NLR for the prediction of IVIG resistance compared with the Egami score, Kobayashi score, CRP, albumin, and CAR. However, the sensitivity and specificity of NLR was 72.4% (Table 4). Insufficient sensitivity leads to overtreatment and carries a risk of adverse effects of the treatment. Early identification of patients who are likely to develop IVIG resistance is a challenge; it is easier to identify them after initial therapy [9, 27]. Several factors, such as IVIG resistance, responsiveness, and disease relapse, are associated with CAL complications [28]. Therefore, risk stratification both before and after initial therapy for KD is important for the prevention of severe CALs [5].

The limitations of this study include its small sample size and retrospective study design. A study regarding the predictors for CAL development could not be conducted because of the small sample size of patients with CAL development.

5. Conclusion

The NLR is an independent predictor for both IVIG-resistant patients and those requiring rescue therapy for resistance without complications before initial acute-phase treatment. However, the sensitivity was below 75%. Insufficient sensitivity leads to overtreatment and carries a risk of adverse effects from the treatment. Therefore, risk stratification both before and after initial therapy for KD is important for the prevention of severe CALs.

Compliance with ethical standards

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Disclosure of conflict of interest

None.

Statement of ethical approval

Our institutional ethics committee approved the study protocol and waived the requirement of patient consent because of the retrospective nature of the study.

Statement of informed consent

Our institutional ethics committee waived the requirement of patient consent because of the retrospective nature of the study.

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