Neonatal and Pediatric Medicine
ISSN: 2572-4983
Research Article Open Access

Prediction of Resistant to Intravenous Immunoglobulin (IVIG) Treatment in Patients with Kawasaki Disease in the Tertiary Care Hospital

Sarinrath Charoonrochana[1*], Kittipol Klaiklueng[2] and Rattawanlop Somanundana[2]

[1]*Department of Pediatrics, Bhumibol Adulyadej Hospital, The Directorate of the Medical Services, The Royal Thai Air Force, Bangkok, Thailand*

[2]*Pediatric Cardiology Division, Bhumibol Adulyadej Hospital, The Directorate of the Medical Services, The Royal Thai Air Force, Bangkok, Thailand*

Abstract

Background: Kawasaki disease (KD) is an acute autoimmune systemic vasculitis disease that mainly occurs in infancy and younger children. It has the potential to cause coronary artery lesions (CALs) develop in up to 20-25% of patients with untreated KD caused morbidity and mortality in children worldwide especially in Asia.

Objective: To determine the predictive factors of IVIG resistant Kawasaki disease in Thailand.

Method: A retrospective descriptive study. Patient charts of all patients who had newly diagnosed of KD in Bhumibol Adulyadej Hospital, Thailand between January 2010 and December 2020 were reviewed. The protocol was approved by the ethic review committee.

Results: A total of 102 subjects met the inclusion criteria and were enrolled into the study, including 17 cases of IVIG resistant (17/97, 28.5%) and 80 cases of IVIG responder (80/97, 71.4%).Demographic and laboratory characteristics were obtained. Male gender has greater in number in IVIG resistant group. Average age is 27 months and IVIG resistant tends to have age below 6 months old. Two variables were significantly lower in IVIG-resistant group than IVIG-responder group, including serum albumin (3.01 ± 0.51 vs. 3. 48 ± 0. 49 g/ dL, p-value=0.01) and serum sodium (133. 24 ± 3.43 vs. 135.79 ± 3.19 m Eq/ L, p-value=0. 01) meanwhile age at time of diagnosis less than 6 months (29.4% vs. 8.75%, p-value=0. 02) and serum ALT (78.29 ± 74.19 vs. 71.01 ± 80.19 IU/L, p-value=0.02) were significantly higher in IVIG-resistant group than IVIG-responder group.

Conclusion: The predictive factors of our study by univariate analysis included age below 6 months, serum albumin<3.5 g/dL, serum sodium<135 mmol/L and high serum ALT ≥ 45 IU/L. The principal findings in our predictive model is the scoring system for predicting IVIG-resistant patients in Thai population, the scoring system includes total peripheral WBC count>18,000 mm3 (1 point), serum albumin<3.5 g/dl (1 point) and serum ALT ≥ 45 IU/L (1.5 points), and a total score equal 2 points and higher yielded a sensitivity and a specificity of 82.35% and 62.50%, respectively for IVIG resistance prediction, who require more close monitoring which may help physicians make more rational decisions regarding an initial treatment of KD and be the candidates for additional therapies. Our study is similar to previous studies in Japan, a risk scoring system prior to administrate IVIG.

Keywords: Kawasaki disease; IVIG resistant; Young children

Introduction

Kawasaki disease (KD; also called mucocutaneous lymph node syndrome and Kawasaki syndrome) is an acute autoimmune systemic vasculitis disease that mainly occurs in infancy and younger children between 6 months to 5 years of age. The acute illness is self- limited and characterized by fever>5 days and at least 4 of the followings; bilateral non exudative bulbar conjunctivitis, changes in lips and oral mucosa, polymorphous rash, cervical adenopathy (greater than 1.5 cm), and changes in peripheral extremities, including swollen hands and feet, red and edematous palms and soles, and later subungual peeling. The definitive etiology remains unclear but some studies found some genetic factors and familial predisposition to KD [1].

Respectively while the incidence of KD in Thailand ranged from 2.14 to 3.43 cases per 100,000 children under 5 years and has become the leading cause of acquired heart disease among children in Thailand [2].

The autopsy studies of fatal cases have clearly demonstrated that inflammation occurs in multiple organs and tissues in KD, although the coronary artery lesions (CALs) are the most clinically significant aspect of the illness includes coronary artery dilatation, coronary aneurysm, coronary fistula, myocardial infarction, and thus sudden dead. The respiratory, gastrointestinal, dermatologic, urinary, nervous and lymphoreticular systems can all be involved [3].

The risk of CALs develop in approximately 20%-25%in children with KD who are not early treatment with high- dose intravenous immunoglobulin (IVIG) and high-dose aspirin, the appropriate treatment in patients who respond well to IVIG have the better chance to decrease the risk of CALs to 3%-5% [4].

The early diagnosis and treatment with IVIG within 10 days of fever onset is the crucial management in patients with KD. Based upon prospective, multicenter treatment trials of IVIG optimal therapy is 2 g/kg with high- dose aspirin (80-100 mg/kg/day) as soon as possible after diagnosis during the acute febrile phase of illness, followed by low-dose aspirin (3-5 mg/kg/day) until follow-up echocardiograms indicate a lack of coronary abnormalities are the current standard treatment in KD [5]. Approximately 10%-20% of patients with KD were IVIG- resistant or non- responder and defined as the KD patients

***Corresponding author:** Charoonrochana S, Department of Pediatrics, Bhumibol Adulyadej Hospital,The Directorate of the Medical Services, The Royal Thai Air Force, Bangkok, Thailand, E-mail: thoy21@hotmail.com

Received: July 17, 2021; **Accepted:** Auugst 31, 2021; **Published**: September 07, 2021

Citation: Charoonrochana S, Klaiklueng K, Somanundana R (2021) Prediction of Resistant to Intravenous Immunoglobulin (IVIG) Treatment in Patients with Kawasaki Disease in the Tertiary Care Hospital. Neonat Pediatr Med S8: 005.

with persistent or recurrent fever at least 36 hours after the end of IVIG infusion. Furthermore, many studies have shown that these patients are at increased risk of developing CALs [5].

The previously classic risk factors from three Japanese risk-scoring systems in predicting outcomes of KD such as Kobayashi, Egami and Sano risk scores include young ages, high C-reactive protein, high peripheral neutrophil percentage, high serum alanine transaminase (ALT), high bilirubin level, low blood hemoglobin, low serum albumin and low serum sodium are widely accepted to predict IVIG resistance however the usefulness, effectiveness and accuracy for prediction IVIG resistance among patients with KD remains challenging in Thailand. The main objective of our study was to develop and validate the predictive factors for IVIG-resistant KD in Thailand.

Materials and Methods

Study population

A single-center-based retrospective study, reviewed 102 consecutive pediatric patients under 15 years of age who were hospitalized and treated in department of pediatrics at Bhumibol Adulyadej Hospital between January 2010 and December 2020 with newly diagnosis of KD according to the American Heart Association (AHA) guidelines. The study protocol was reviewed and approved by the Ethics Committee of Bhumibol Adulyadej Hospital Affiliated, and with its approval. Sample size was calculated by using single group proportion with 0.1 alpha (α) error. There are at least 68 cases a good for statistical significant. The protocol was approved by the ethic review committee (IRB 76/63).

All patients were receiving initially high-dose IVIG (2 g/kg) as a single 8-12 hours infusion according to the AHA recommendation combined with high- dose aspirin (80-100 mg/kg/day) every 6 hours. After 36 hours at the end of the first dose of IVIG infusion, the patients were grouped as IVIG- responder or IVIG- resistant (non-responder) KD. For a refractory case to the initial treatment with the 1st dose of IVIG, repeated dose of IVIG were provided and methylprednisolone pulse therapy or infliximab were provided after second-dose of high-dose IVIG in patients with re-fever.

Data collection

Data referring to demographic characteristics, clinical manifestations, laboratory examination and echocardiographic results were obtained including age in month at the time of diagnosis, gender, number of days with fever prior to initial treatment with IVIG, presence and degree of CALs, and ineluctable related clinical manifestations.

Two- dimensional echocardiographic data was obtained at the time of diagnosis prior to initial treatment and at 6 weeks and 6 months after treatment. All dimensions of coronary arteries were obtained by a standardized protocol and performed by a single pediatric cardiologist.

Presence of CALs was defined as coronary artery diameter more than 2.5 mm. in patients aged less than 3 years old, more than 3. 0 mm. in patients aged 3 and 9 years old and more than 3.5 mm in patients older than 9 years old. As for the degree of CALs (D- CALs), localized dilatation with internal diameter (ID) less than 4 mm the dilatation with ID between 4 mm and 8 mm and the dilatation with internal diameter more than 8 mm were defined as slight CALs, moderate CALs and severe CALs, respectively.

Laboratory data were obtained, including hemoglobin (Hb), Hematocrit (Hct), white blood cell (WBC) count and morphology, percentage of lymphocyte (LYM) count, percentage of neutrophil (PMN) count, percentage of monocyte and platelet (PLT) counts, serum albumin, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum total and direct bilirubin, serum blood urea nitrogen (BUN) and creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum sodium, serum potassium and serum chloride. All those laboratory variables were routinely obtained in our clinical practice and recorded at the time of diagnosis.

For using the previous models, we kept the predictors in those models and re-estimate the coefficients with the current data set to build the models. Predictive ability of the new model was compared with the previous models including [6-8] scoring systems from Japan and Yang prediction model from China.

Statistical analysis

SPSS statistical software package, version 27. OJ (SPSS, Chicago, USA) was used for statistical analyses. Continuous variables were summarized using mean and standard deviation (mean ± SD) or using frequencies (%) of patients to describe categorical variables. Student's t-test and Mann-Whitney U tests for continuous data and qui square test for categorical data were used to compare variables between the 2 groups. For all analyses a two- sided probability value below 0.05 (p-value< 0.05) was considered to indicate statistical significance. Results and significance values are summarized in the relevant tables.

Variables selected by the univariate analysis with p-value< 0.05 were applied for multivariate logistic regression to explore independent risk factors for IVIG resistance. To construct the scoring system, the score of independent risk factors were determined by the odd ratios (OR). The cut-off point was selected by the receiver-operator characteristic (ROC) curves and the sensitivity and specificity of the scoring system were analyzed

Results

Demographic and clinical manifestations

A total 102 consecutive pediatric patients diagnosed with Kawasaki disease was excluded due to lack of data for 5 patients. A total of 97 patients which were 60 male patients and 37 female patients (male-to-female ratio 1.62) met the inclusion criteria according to the AHA guidelines and were enrolled into our study (Figure 1). The age ranged was 1 to 144 months with a median of 27.3 months. Eighty (80) patients occurred in IVIG-responder group (80/97, 71.4%) included 46 male patients (46/80, 57.5%) and 34 female patients (34/80, 42.5%) with a median of 28 months. Thirty-four (34) patients were diagnosed with incomplete KD (35%). Seventeen (17) patients occurred in IVIG-resistant group (17/97, 28.5%) included 14 male patients (14/17, 82.4%) and 3 female patients (3/17, 17.6%) with a median of 21 months. No case was recurrent KD after at least 3 years follow-up including no history of KD in siblings (Table 1).

Univariate analysis

According to the univariate analysis (Table 2), 4 variables were selected and weighted proportionally to their respective odds ratio for IVIG-resistant. Two variables were significantly lower in IVIG-resistant group than IVIG-responder group, including serum albumin (3.01 ± 0.51 vs. 3.48 ± 0.49 g/dL, p-value=0.01) and serum sodium (133.24 ± 3.43 vs. 135.79 ± 3.19 m Eq/L, p-value=0.01) meanwhile age at time of diagnosis less than 6 months (29.4% vs. 8.75%, p-value=0.02) and

serum ALT (78.29 ± 74.19 vs. 71.01 ± 80.19 IU/L, p-value=0.02) were significantly higher in IVIG-resistant group than IVIG-responder group.

Mean age of IVIG-responder group was higher than IVIG-resistant group but no statistical significance (21 ± 26.16 vs. 28.56 ± 24.98 months, p-value=0.30) as shown in Table 1.

There was no difference of gender among responder and resistant groups. The remaining predictive values among both groups were comparable as shown in Table 1.

Multivariate analysis

We explored multivariate predictive factors for IVIG resistance

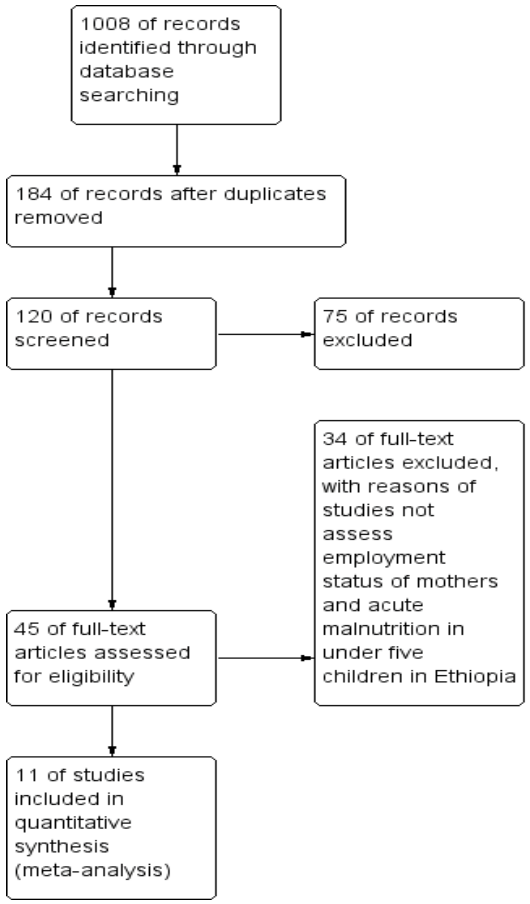

Figure 1: Shown 102 patients was diagnosed Kawasaki disease, 5cases with missing data was excluded from our study, Remained 97 patient with IVIG resistant consist 17 patients and IVIG responders consist 80 patients.

Characteristics	IVIG responder	IVIG resistant	p-value
	N=80	N=17	
Mean age (months)	28.5 ± 24.9	21 ± 26.1	0.308
Age less than 6 months	7 (8.7)	5 (29.4)	0.027
Male gender	46 (57.5)	14 (82.3)	0.067
Hematocrit (<35%)	65 (81.2)	16 (94.1)	0.222
Hemoglobin (<10 g/dL)	31 (38.7)	8 (47.0)	0.527
WBC (>18,000cell/mm^3)	26 (32.5)	9 (52.9)	0.117
Neutrophil (≥ 80%)	8 (10.0)	2 (11.7)	0.828
Platelet (≤ 350,000 cell/mm^3)	28 (35.0)	7 (41.1)	0.631
Albumin **(**<3.5 g/dL**)**	36 (45.0)	14 (82.3)	0.01
Total bilirubin (≥ 0.7 mg/dL)	14 (17.5)	3 (17.6)	0.988
AST (≥ 80 IU/L)	12 (15.0)	4 (23.5)	0.394
ALT **(**≥ 45IU/L**)**	36 (45.0)	13 (76.4)	0.025
Sodium **(**<135 mmol/L**)**	30 (37.5)	12(70.58)	0.017
Chloride (<96 mmol/L)	34 (42.5)	4 (23.5)	0.154
ESR (≥ 40 mm/hr)	53 (66.3)	11 (64.7)	0.903
CRP (≥ 60 mg/dL)	49 (61.2)	14 (82.3)	0.109
CAL[b] before treatment	29 (36.3)	13 (76.4)	0.005
[b]Bilirubin			

Table 1: Baseline demographic characteristics among responder (n=80) and resistant (n=17) to intravascular immunoglobulin (IVIG).

Characteristics	Odds ratio	95 % Confidence Interval	p-value
Mean age (months)	0.99	(0.96-1.01)	0.308
Age less than 6 months	4.35	(1.18-15.94)	0.027
Male gender	3.45	(0.92-12.96)	0.067
Hematocrit (<35%)	3.69	(0.45-30.06)	0.222
Hemoglobin(<10 g/dL)	1.41	(0.49-4.03)	0.527
WBC (>18,000 cell/mm^3)	2.34	(0.81-6.75)	0.117
Neutrophil (≥ 80%)	1.2	(0.23-6.23)	0.828
Platelet (≤ 350,000 cell/mm^3)	1.3	(0.45-3.79)	0.631
Albumin **(**<3.5 g/dL**)**	5.7	(1.52-21.4)	0.01
Total bilirubin (≥ 0.7 mg/dL)	1.01	(0.26-3.99)	0.988
AST (≥ 80 IU/L)	1.74	(0.49-6.26)	0.394
ALT **(**≥ 45 IU/L**)**	3.97	(1.19-13.24)	0.025
Sodium **(**<135 mmol/L**)**	4	(1.28-12.47)	0.017
Chloride (<96 mmol/L)	0.42	(0.12-1.39)	0.154
ESR (≥ 40 mm/hr)	0.93	(0.31-2.80)	0.903
CRP (≥ 60 mg/dL)	2.95	(0.78-11.11)	0.109
CAL[b]before treatment	5.72	(1.7-19.16)	0.005
[b]Bilirubin			

Table 2: Baseline characteristics of participants in our study.

Risk factors	Intravascular immunoglobulin (IVIG)		Multiple analysis		Coefficient	Risk score
	Responder	Resistant	Adj OR (95 % CI)	p- value		
WBC	26 (32.5)	9 (52.9)	2.34	0.117	1.35	1
(>18,000 cell/mm^3)			(0.81-6.75)			
Serum albumin	36 (45.0)	14 (82.3)	5.7	0.01	1.63	1
(<3.5 g/dL)			(1.52-21.4)			
Serum ALT	36 (45.0)	13 (76.4)	3.97	0.025	1.76	1.5
(≥45 IU/L)			(1.19-13.24)			

Table 3: Risk factors for predicting IVIG-resistant by multivariate analysis.

in our data (Table 3). All study subjects were analyzed, the results indicated that independent risk factors for IVIG resistance include only 3 variables; high total peripheral WBC count>18,000 mm^3 (OR=2.34, p-value=0.117 and c-statistic 1.35), high serum ALT>45 IU/L (OR=3.97, p-value=0.025 and c-statistic 1.76) and low serum albumin<3.5 g/dl. (OR=5.70, p-value = 0.010 and c-statistic 1.63), were the most consistent multivariate models.

Scoring system for IVIG resistant prediction

To construct the scoring system (Tables 4-6), both of total peripheral WBC count (>18,000 mm^3) and serum albumin (<3.5 g/dL) were given 1 point while serum ALT (>45 IU/L) was given 1.5 points. The total scores were calculated for each KD patient. ROC analysis indicated that the area under the curve (AUC) was 0.79 with 95% CI, 0.69-0.89; p-value<0.01 and a cut-off score of 2 points or higher with the sensitivity of 82.35% and specificity of 62.50% to predict IVIG resistance.

Discussion

KD is an acute autoimmune systemic vasculitis disease that commonly affects the small and medium-size arteries, especially coronary arteries. CALs are the most serious complications of KD, which occur in approximately 20-25% in children who are not early treatment with IVIG [1]. In our study, the frequency of developing CALs was 29% in IVIG resistant group.

Some previous studies shown CALs at onset of acute phase developed more often in IVIG resistant group [2]. All our patients received IVIG administration as initial treatment the relationship between IVIG resistant and CALs in our study at prior treatment has significant association but no association at 2nd(6 weeks) and 3rd times (6 months) of echocardiogram follow-up after initial treatment, this might be considering that nonresponse may reflect only severity of ongoing inflammation in acute phase whereas development of CAAs might be affected by both ongoing inflammation and hemodynamics after initiation of treatment [9].

Over 80% of occurs in infancy and younger children between 6 months to 4 years of age, rarely reported in adolescents and adults [10]. In our study shown the mean age of 27.3 months and KD patients with age less than 6 months occur only 13.4% (13/97) suggests that most infants with KD are protected by transplacental maternal immunity.7 In addition, we also found KD patients with IVIG resistant group was younger than IVIG responder group and the frequency of KD patients with age younger than 6 months were higher in IVIG resistant group than IVIG responder group significantly [11].

Many previous studies shown evidence of low serum sodium, low serum albumin and high serum ALT all strongly predicted IVIG unresponsiveness while in our study showed only low serum albumin and high serum ALT.

Risk score	Intravascular immunoglobulin (IVIG)		Total
	Responder	Resistant	
<2	50 (62.5)	3 (17.6)	53 (54.6)
≥ 2	30 (37.5)	14 (82.4)	44 (45.4)
Total	80	17	97 (100.0)

Table 4: Risk scoring for predict IVIG resistant group.

Nakamura study noted that hyponatremia might be the most useful to predict giant coronary aneurysms (diameter 8 mm and higher) caused by KD. The relationship between hyponatremia and severity of KD might involve permeability of the endothelium, dehydration, duration of fever and severity of illness but pathogenesis of hyponatremia in KD remains clearly understood, possible mechanism including the syndrome of inappropriate antidiuretic syndrome (SIADH), hyponatremic dehydration and hypo-osmolar fluid intake [12].

Kobayashi scoring system is now widely used among Japanese populations to predictthe risk of IVIG resistance but unfortunately it did not accurately predict outcomes in non-Japanese populations. Hepatic impairment was frequent found in the patients with KD. This phenomenon caused by activated cytokine-natural killer cells during acute phase of inflammatory process in liver sinusoids caused hepatocytic injury in KD [6] Both Egami and Kobayashi scoring systems; suggest that high level of serum ALT was the predictor of severity of KD. The cut-off points of Egami and Kobayashi risk scoring were more than 80 and 100 IU/L, respectively, while our study, the cut-off point was only equal and higher than 45 IU/L which is less than previous studies.

In our study showed that hypoalbuminemia (serum albumin<3.5 g/dl) isthe predictor for IVIG resistance, this can explained by the pathophysiology of KD in acute phase caused by increased permeability of the vessels due to inflammatory mediators so hypoalbuminemia reflect the more severe leakage of plasma protein and from hepatic impairment reduced the synthesis of albumin because cytokine-activated natural killer cells accumulate at inflammatory lesions in the acute phase of KD, these activated natural killer cells might accumulate in vascular endothelium and along liver sinusoids where they would be likely to participate in hepatocytic injury. IVIG resistance patients tend to have more severe vascular leakage and liver impairment according to lower serum albumin. Nowadays in Japan, low albumin level is used as one of the risk factors in selection of candidates for IVIG treatment of KD [13].

Principal findings of our study to develop and validate new prediction values were that IVIG resistant could be stratified to lower the risk of progress sequel of CAAs (Table 5). Nowadays, there were several prediction models for IVIG resistant, the risk factors including age below 6 months; IVIG treatment within 4 days of illness; abnormal the echocardiographic results prior treatment; high C-reactive protein, high serum ALT, high serum AST, high percentage of neutrophils, low serum sodium and low serum hemoglobin [14-17]. Our predictive model is the scoring system for predicting IVIG-resistant patients in Thai population, the scoring system includes total peripheral WBC count>18,000 cu.mm. (1 point), serum albumin<3.5 g/dl (1 point) and serum ALT>45 IU/L (1.5 points), and a total score equal 2 points and higher yielded a sensitivity and a specificity of 82.35% and 62.50%, respectively for IVIG resistance prediction (Table 5 and Figure 2).

Study limitation

Five cases with missing file data or with a diagnosis other than complete KD were excluded from our study at the beginning.

Predictive factors	Egami	Kobayashi	Sano	Our study
CRP*(mg/dL)	>8	>10	>7	
Age (month)	<6	>12		
BILI$^{\delta}$ (mg/dL)			>0.9	
AST (IU/L)			>200	
ALT (IU/L)	≥ 80	≥ 100		≥ 45
Sodium (mmol/L)		≤ 133		
Platelet counts (cell/mm^3)	≤ 300,000			
Percentage of neutrophils (%)		≥ 80		
Albumin (g/dL)				<3.5
WBC (cell/mm^3)				>18,000
*C-reactive protein, $^{\delta}$Bilirubin				

Table 5: Risk scoring differences among the clinical studies.

Predictive validity	
Sensitivity	82.35 (74.77-89.94)
Specificity	62.50 (52.87-72.13)
Positive predictive value	31.82 (22.55-41.09)
Negative predictive value	94.34 (89.74-98.94)
Likelihood ratio (+)	2.20 (1.53-3.14)
Likelihood ratio (-)	0.28 (0.10-0.80)
Accuracy	65.97 (55.66-0.75)
AUROC	0.79 (0.69-0.89)

Table 6: Predictive validity for resistant to intravascular immunoglobulin (IVIG).

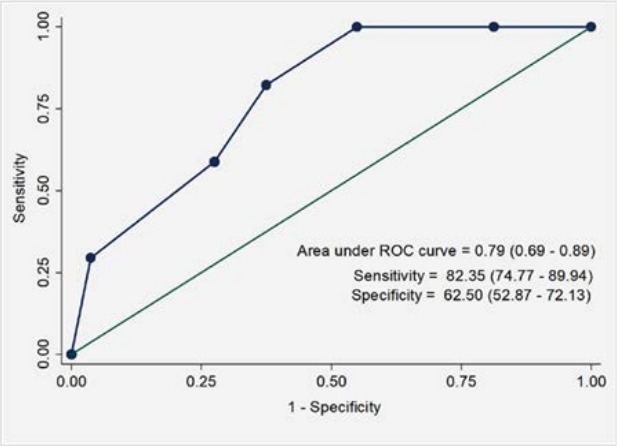

Figure 2: ROC and AUC of the prediction models for IVIG-resistance. The new predictive model for IVIG resistance show an AUC of 0.79.

Conclusion

In conclusion, the predictive values that we note similar to previous studies in Japan, a risk scoring system based on demographic and laboratory characteristics prior to administrated IVIG can accurately prediction the high-risk patients of IVIG resistant seen in Table.2, who require more close monitoring which may help physicians make more rational decisions regarding an initial treatment of KD and be the candidates for additional therapies.

Acknowledgements

The authors would like to thank to (1) Gp.Capt. Napaporn Jiraphongsa M.D., M.Sc., Division of Clinical Epidemiology, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok, Thailand (2) Gp.Capt. Sasawan Chinratanapisit M.D. Ph.D., Division of Allergy & Immunology, Department of Pediatrics, Bhumibol Adulyadej Hospital, Bangkok, Thailand. (3) Ms. Pangpawinee Saybung and (4) Ms. Suwittra Huanraluck for help on statistical analysis of the data. The authors acknowledged the help of Assoc. Prof.Wg. Cdr. Komsun Suwannaruk M.D. and Assoc.Prof. Dr. Kornkarn Bhamarapravatana Ph.D. Department of Preclinical Sciences, Faculty of Medicine, Thammasat University, Pathumthani, Thailand for their assistance in data analysis and manuscript preparation.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Beth SM, Sundel RP (2016) Kawasaki Disease. Textbook of Pediatric Rheumatology 467-483.
2. Durongpisitkul K, Sangtawesin C, Khongphatthanayopthin A, Panamonta M, Sopontammarak S, et al. (2006) Epidemiologic study of kawasaki disease and cases resistant to IVIG therapy in Thailand. Asian Pac J Allergy Immunol 24: 27-32.
3. Yeung RSM (2012) Kawasaki Disease. Textbook of Clinical Pediatrics 1675-1684.
4. Wei M, Huang M, Chen S, Huang G, Huang M, et al. (2015) A multicenter study of intravenous immunoglobulin non-response in kawasaki disease. Pediatr Cardiol 24:7-19.
5. Sophie D, Doyle SL, McMahon CJ (2019) Refractory kawasaki disease: Diagnostic and management challenges. Pediatric Health Med Ther 10: 131-139.
6. Kobayashi T, Fuse S, Sakamoto N, Mikami M, Ogawa S, et al. (2016) A new Z score curve of the coronary arterial internal diameter using the lambda-mu-sigma method in a pediatric population. J Am Soc Echocardiogr 29: 794-801.
7. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, et al. (2008) Prediction of non- responsiveness to standard high-dose gamma-globulin therapy in patients with acute kawasaki disease before starting initial treatment. J Pediatr 166: 131-137.
8. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, et al. (2006) Prediction of resistance to intravenous immunoglobulin treatment in patients with kawasaki disease. J Pediatr 149: 237-240.
9. Kumar PR, Jindal AK, Guleria S, Singh S (2019) An update on treatment of kawasaki disease. Curr Treatm Opt Rheumatol. 5: 36-55.

10. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, et al. (2004) Diagnosis, treatment, and long-term management of kawasaki disease. Circulation. 110: 2747-2771.

11. Kuo CH, Liang CD, Wang CL, Yu CR, Hwang KP, et al. (2010) Serum albumin level predicts initial intravenous immunoglobulin treatment failure in kawasaki disease. Acta Paediatr 99: 1578- 1583.

12. Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, et al. (2008) Increasing incidence of kawasaki disease in Japan: Nationwide survey. Pediatr Int 50:287-90.

13. Terai M, Honda T, Yasukawa K, Higashi K, Hamada H, et al. (2003) Prognostic impact of vascular leakage in acute kawasaki disease. Circulation 108: 325-330.

14. Rigante D, Andreozzi L, Fastiggi M, Bracci B, Natale M, et al. (2016) Critical overview of the risk scoring systems to predict non-responsiveness to intravenous immunoglobulin in kawasaki syndrome. Int J Mol Sci 17: 278.

15. Rowley, Anne H, Shulman ST (2010) Pathogenesis and management of kawasaki disease. Expert Rev Anti Infect Ther 8: 197-203.

16. Seki S, Habu Y, Kawamura T, Takeda K, Dobashi H, et al. (2000) The liver as a crucial organ in the first line of host defense: The roles of Kupffer Cells, Natural Killer (NK) Cells and NK1.1 Ag+ T Cells in T Helper 1 Immune Responses. Immunol Rev 174: 35-46.

17. Yang L, Wu H, Jin X, Zheng P, Hu S, et al. (2011) Study of Cardiovascular Disease Prediction Model Based on Random Forest in Eastern China. Scientific Reports. 10.