Evaluation of Egami Risk Scores in Predicting Intravenous Immunoglobulin (IVIG) Resistance in Malaysian Paediatric Population with Kawasaki Disease

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Abstract

Introduction: Egami score has been used in various countries to predict the resistance to intravenous immunoglobulin (IVIG) in paediatric patients with Kawasaki Disease (KD), but it has not been validated in Malaysia.

Objective: To evaluate the use of Egami Scores in predicting IVIG resistance in the Malaysian paediatric population with KD.

Methods: Retrospective data of children admitted for KD and received IVIG within 10 days of the onset of illness from 2008 to 2015 was collected from two hospitals in Kedah, Malaysia. IVIG resistance was defined as fever more than 37.5ºC for more than 36 hours or recurrent fever following a period of defervescence after the administration of initial IVIG. Egami scores were assigned based on patients' demographic and laboratory parameters. Patients with Egami scores of 0 to 2 were categorised as low risk while patients with 3 points and above were categorised as high risk of IVIG resistance.

Results: Egami risk scores were calculated for 57 KD patients with complete data. Nine of these patients (15.8%) had IVIG resistance while 48 were IVIG responders. The median Egami scores for IVIG resistant patients and IVIG responders were 3 (inter-quartile range (IQR) 1-3) and 1 (IQR 1-2) respectively (p=0.055). Among the nine IVIG resistant patients, three (33.3%) were categorised in the low-risk group and six (66.7%) were in the high-risk group. Among the IVIG responders, 37 patients (77.1%) were categorised as having low risk for IVIG resistance and 11 patients (22.9%) were in the high-risk group (p=0.015). Therefore, the Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, positive predictive value of 35.3% and negative predictive value of 92.5%.

Conclusion: The Egami score was able to predict IVIG resistance but it may not be sensitive enough to be applied as the only method of prediction.

Keyword: Egami score, IVIG resistance, Kawasaki disease, Kawasaki prediction score

NMRR ID: NMRR-16-110-29114(IIR)

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Introduction

Kawasaki disease (KD) is an acute inflammatory syndrome predominantly affects children younger than 5 years old (1). It is characterised by five days of fever with other clinical features, including non-exudative bilateral conjunctival injection, erythema of the lips and oral cavity, atypical rash, oedema or erythema of hands and feet, and cervical lymphadenopathy (2). The aetiologies of KD remain unknown, but it has been reported to substitute acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries (3). The potentially fatal complications of KD may include coronary artery (CA) dilatation and aneurysm formation (4).

In principal, the primary objective in the treatment of acute KD is to minimise the risk of developing CA lesions and prevent further complications (5). It has been suggested that prompt treatment using high dose (2g/kg) intravenous immunoglobulin (IVIG) during the initial 10 days of illness will provide immediate

suppression of the acute-phase inflammatory reaction in KD, resulting in lower incidence of CA aneurysms and less coronary damage (6,7). However, several studies also highlighted that 13 to 21 percent of patients receiving IVIG tend to develop persistent fever or recrudescent upon completion of the initial IVIG administration. Such patients are considered to have IVIG resistance or refractory KD (8-11), and these patients have the greatest risk of developing CA aneurysms (12, 13). Thus, early identification of patients who has high tendency of developing IVIG resistance is important in order to provide alternative options such as the use of other anti-inflammatory therapies, including corticosteroids (14) or anti-tumour necrosis factor (TNF)-α therapy (15).

Evaluation of the likelihood of patients developing IVIG resistance can be performed using several established risk scoring algorithm, including the Fukunishi score(16), Egami score(8), Kobayashi score(9), and Sano Score(10) from Japan, San Diego score(13) from America and the most recent Formosa score(17) from Taiwan. The duration of illness prior to initial treatment, age, inflammatory markers, liver enzyme and blood counts are among the common variables included in most of the scoring system. Kobayashi and Sano scores additionally account for the level of aspartate aminotransferase (AST). A recent study by Sleeper *et al.* showed that when all the three existing Japanese scoring systems (Kobayashi Score, Egami Score and Sano score) were used to predict IVIG resistance in the North American population, the scores displayed good specificity but low sensitivity of less than 45%. Of which, the Egami scores demonstrated the highest sensitivity and specificity as compared to the other scoring methods (18).

To explore the potential of using Egami score to predict IVIG resistance in the local setting, it is important to externally validate the Egami score in the multi-ethnic Malaysian population. Hence, in this study, we aimed to evaluate the use of Egami Scores in predicting IVIG resistance in the Malaysian paediatric population.

Methods

A retrospective study was performed using the medical records of KD patients who were admitted between 2008 to 2015 in the two selected general hospitals at the northern region of Malaysia, namely the Sultan Abdul Halim Hospital and Sultanah Bahiyah Hospital. The classification of KD patients in this study was based on the clinical diagnosis in accordance to the modified American Heart Association criteria, which includes five or more days of fever and the presence of at least four out of the five principle clinical features (non-exudative bilateral conjunctival injection, erythema of the lips and oral cavity, atypical rash, oedema or erythema of hands and feet, and cervical lymphadenopathy), or the presence of less than four clinical features when CA disease is detected through echocardiography or coronary angiography (19).

KD patients who received the initial dose of 2g/kg IVIG within 10 days of the onset of illness were included into the study. Patients were categorised as IVIG resistance with the presence of fever more than 37.5ºC lasting more than 36 hours or recurrent fever following a period of defervescence after the administration of initial IVIG. The complete data on admission details, age, sex, duration of fever (in days), complete blood count, erythrocyte sedimentation rate (ESR), albumin, total bilirubin, alanine aminotransferase (ALT), C-reactive protein (CRP) and echocardiogram results were obtained and screened. Patient's CA status was confirmed upon echocardiogram done during the acute phase and any repeated echocardiogram at six to eight weeks period by a certified paediatric cardiologist.

Egami scores were assigned based on patients' demographic and laboratory parameters. In the Egami algorithm to predict IVIG resistance, scores were recorded in the scale of 0 to 5 points. Patients with Egami scores of 0 to 2 were categorised as having low risk of IVIG resistance while patients with 3 points and above were categorised in the high-risk group. The Egami scores were assigned according to the following criteria: ALT ≥ 80IU/L (2 points), day of illness at initial IVIG day 4 or earlier (1 point), CRP ≥ 8mg/dL (1 point), platelet counts ≤ $30.0 \times 10^4/mm^3$ (1 point) and age ≤ 6 months (1 point).

Statistical Package for the Social Science (SPSS) Version 21.0 was used for data analysis. Demographic and descriptive data were presented as mean with standard deviation (SD) or medians with inter-quartile range (IQR) for continuous data, and frequency (n) with percentage (%) for categorical data. Student T-test was used to compare the resistance to IVIG for normally distributed variables and Mann-Whitney U test was used for the non-normally distributed variables. Fisher exact test and Chi Square test were applied to compare the categorical risk score (number of points) distributions by IVIG re-treatment status. Statistical significance was set at 0.05. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the score were calculated.

Results

From 2008 to 2015, there were a total of 99 patients with the diagnosis of KD who received IVIG. However, only 88 patients were included in this study. Seven patients were excluded as IVIG were given only after 10 days of illness, two were excluded following incomplete data on temperature charting, and another two were excluded due to lack of record on the criteria fulfilment for Kawasaki Disease.

Figure 1 showed the number of KD and IVIG resistance cases from 2008 to 2015. The highest number of KD cases were recorded in 2014 and 2015, with 16 and 15 cases respectively. Of the total included patients, there were 12 patients (13.6%) with IVIG resistance. Seven patients had persistent fever (temperature >37.5ºC) for more than 36 hours and 5 patients had recurrent fever after a period of defervescence.

In the baseline characteristics of study populations (Table 1), a vast majority were Malays (73.9%) followed by Chinese (20.5%) and Indians (5.7%). In terms of gender, there were higher proportion of males both in the IVIG resistance group (83.3%) and IVIG responder group (60.5%). The median age for IVIG resistance group were found to be 8.5 months whereas the IVIG responder group was 12 months.

Figure 1: The number of KD and IVIG resistance in two northern Malaysia hospitals from 2008 to 2015 (n=88)

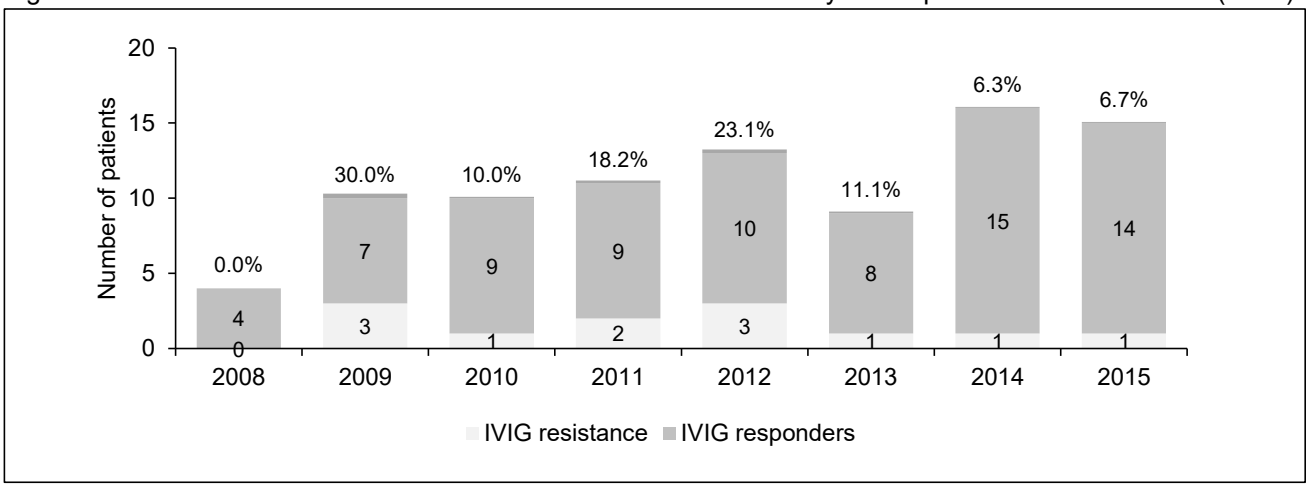

Table 1: The baseline characteristics of IVIG resistance and IVIG responders (n=88)

Variables	IVIG resistance (n=12)	IVIG responders (n=76)	P-value
Age at diagnosis, month, median (IQR)	8.5 (4.8-34.3)	12.0 (8.3-27.0)	0.327 *
Illness days of initial IVIG, median (IQR)	6 (5-7)	6 (5-8)	0.829 *
Gender, male:female	5:1	1.5:1	0.198 **
Type of Kawasaki disease, n (%)			1.00 **
Complete	10 (83.3)	63 (82.9)	
Incomplete	2 (16.7)	13 (17.1)	
Race, n (%)			0.724 **
Malay	10 (83.3)	55 (72.4)	
Non-Malay	2 (16.7)	21 (27.6)	
Presenting symptom, n (%)			
Conjunctivitis	11 (91.7)	64 (84.2)	0.685 **
Rashes	9 (75.0)	67 (88.2)	0.359 **
Extremities changes	9 (75.0)	49 (64.5)	0.744 **
Oral mucosal changes	10 (83.3)	71 (93.4)	0.242 **
Lymphadenopathy	8 (66.7)	63 (82.8)	0.397 **

*Mann-Whitney test; ** Fishers's Exact test
Abbreviation: IVIG – intravenous immunoglobulin; IQR – inter-quartile range

The comparison of the laboratory values between the two groups found that IVIG resistance patients have significantly higher white blood cell count (p=0.038), higher neutrophil percentage (p=0.004), and higher total bilirubin (p=0.022). The lymphocytes, however, was significantly lower in the IVIG resistant group (p<0.001) (Table 2).

Echocardiogram results were available in 85 of the patients. The results showed that more than half of the patients (68.2%) identified to have normal CA. CA dilatation were found in 20% of patients, medium CA aneurysms in 10.6% of patients and 1.2% patients developed giant CA aneurysm. Comparison of the presence of CA aneurysm showed that a significant difference was found between the IVIG resistant group and the IVIG responder group. Significantly higher number of patients (50%) of the IVIG resistant group developed CA aneurysms as compared to the IVIG responders (5.5%) (p<0.001) (Table 3).

Table 2: Laboratory values of IVIG resistance and IVIG responders (n=88)

Variables	IVIG resistance (n=12)	IVIG responders (n=76)	P-value
WBC count (10^9/L) [a]	17.9 (14.5-22.1)	14.0 (11.4-17.5)	**0.038** *
Hemoglobin (g/dL) [b]	10.8 ±1.7	11.0 ± 1.1	0.756 †
Hematocrit (%) [b]	32.1 ± 5.6	33.1 ± 3.5	0.550 †
Platelet (10^9/L) [a]	432 (363-554)	425 (291-510)	0.488 *
MCV (fl) [a]	77.7 (75.0-80.3)	77.6 (75.7-80.8)	0.980 *
MCH (pg) [a]	25.9 (25.2-26.5)	25.8 (24.2-26.7)	0.863 *
MCHC (g/dL) [a]	33.3 (32.7-34.3)	33.0 (32.0-34.0)	0.351 *
Lymphocytes (%) [a]	16.6 (11.1-22.3)	31.3 (21.1-39.6)	**<0.001** *
Neutrophil (%) [a]	74.6 (68.9-80.2)	58.2 (50.8-68.7)	**0.004** *
ESR (mm/h) [b]	71.1 ± 38.1	78.5 ± 27.3	0.474 †
CRP (mg/L) [a]	130.7 (97.2-151.8)	106.2 (57.1-148.4)	0.334 *
Serum Albumin (g/dL) [b]	3.1 ± 0.7	3.3 ± 0.6	0.297 †
Total bilirubin (umol/L) [a]	15.0 (8.4-43)	7.0 (5.0-12.0)	**0.022** *
ALT (IU/L) [a]	88.0 (13.5-110.5)	26.0 (14.5-94.5)	0.605 *
Sodium (mmol/L) [a]	133 (132-136)	134 (132-136)	0.892 *

[a] data presented in median (IQR); [b] data presented in mean (SD); *Mann-Whitney test; †Independent-T test
Abbreviation: IVIG – intravenous immunoglobulin; WBC – white blood cell; MCV – mean cell volume; MCH – mean cell haemoglobin; MCHC – mean cell haemoglobin concentration; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; ALT – Alanine Aminotransferase

Table 3: The presence of CA aneurysms in IVIG resistance and IVIG responders (n=85)

Characteristic	Total (n=85)	IVIG resistance (n=12)	IVIG responders (n=73)	P-value
Presence of CA aneurysms				< 0.001 **
Yes	10 (11.8%)	6 (50.0%)	4 (5.5%)	
No	75 (88.2%)	6 (50.0%)	69 (94.5%)	

** Fisher's Exact test
Abbreviation: IVIG – intravenous immunoglobulin; CA – coronary artery

There were incomplete laboratory data to calculate the Egami scores in 31 patients. Egami risk scores were calculated for 57 patients with complete data. The median Egami score for IVIG resistant patients and IVIG responder were 3 (IQR 1 to 3) and 1 (IQR 1 to 2) respectively (Table 4). The Fisher's Exact test showed that the Egami score was significantly associated with IVIG resistance in our patients (p=0.015). The Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, positive predictive value (PPV) of 35.3% and negative predictive value (NPV) of 92.5% (Table 4).

Egami score was subsequently used to predict patient's CA abnormalities. Patients were classified as having normal CA versus abnormal CA (includes CA dilatations, medium CA aneurysms and giant aneurysms) for comparison (Table 5). Egami score was found to be higher among those in the abnormal CA group, with a median Egami score of 3 (IQR 1-3) as compared to those in the normal CA group with a median score of 1 (IQR 1-2). The sensitivity was 52.2%, the specificity was 85.3%, PPV was 70.6%, and NPV was 72.5%.

To further validate the Egami scores in this study population, patients were further categorised as those presented with CA aneurysms (medium aneurysms and giant aneurysms) and those without CA aneurysms (normal CA and CA dilatation) (Table 6). The median Egami score was 3 (IQR 1-3) for patients with CA aneurysms compared to those with no CA aneurysms with a median Egami score of 1 (IQR 1-2). When the patients were categorised into the low-risk and high-risk groups according to their Egami scores, there was an association with CA aneurysms (p=0.015). The sensitivity was 66.7%, specificity was 77.1%, PPV was 35.3%, and NPV was 92.5%.

Table 4: Comparison of Egami scores in IVIG resistance and IVIG responders (n=57)

Characteristic	Total (n=57)	IVIG resistance (n=9)	IVIG responders (n=48)	Z statistics	P-value
Egami score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.922	0.055 **
Egami score, n (%)					
0	5 (8.8)	0 (0.0)	5 (10.4)		
1	26 (45.6)	3 (33.3)	23 (47.9)		
2	9 (15.8)	0 (0.0)	9 (18.8)		
3	15 (26.3)	6 (66.7))	9 (18.8)		
4	2 (3.5)	0 (0.0)	2 (4.2)		
Risk group, n (%)					**0.015** ǂ
Low risk (0-2)	40 (70.2)	3 (33.3)	37 (77.1) [a]		
High Risk (⩾3)	17 (29.8)	6 (66.7) [b]	11 (22.9)		

** Mann-Whitney Test; ǂ Fisher's Exact Test; [a] Specificity; [b] Sensitivity
Abbreviation: IVIG – intravenous immunoglobulin; IQR – inter-quartile range

Table 5: Comparison of Egami scores by normal CA and abnormal CA status (n=57)

Characteristic	Total (n=57)	Abnormal CA (n=23)	Normal CA (n=34)	Z statistics	P-value
Egami Score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.861	0.063 **
Egami Score n (%)					
0	5 (8.8)	2 (8.7)	3 (8.8)		
1	26 (45.6)	8 (34.8)	28 (52.9)		
2	9 (15.8)	1 (4.3)	8 (23.5)		
3	15 (26.3)	11 (47.8)	4 (11.8)		
4	2 (3.5)	1 (4.3)	1 (2.9)		
Risk group, n (%)					
Low risk (0-2)	40 (70.2)	11 (47.8)	29 (85.3) [a]		**0.002** ǂ
High Risk (≥3)	17 (29.8)	12 (52.2) [b]	5 (14.7)		

** Mann-Whitney test; ǂ Chi-Square test; [a] Specificity; [b] Sensitivity
Abbreviation: CA – coronary artery; IQR – inter-quartile range

Table 6: Comparison of Egami scores by the presence of CA aneurysms (n=57)

Characteristic	Total (n=57)	CA aneurysms (n=9)	No CA aneurysms (n=48)	Z statistics	P-value
Egami Score, median (IQR)	1 (1-3)	3 (1-3)	1 (1-2)	-1.922	0.055 **
Egami Score n (%)					
0	5 (8.8)	0 (0.0)	5 (10.4)		
1	26 (45.6)	3 (33.3)	23 (47.9)		
2	9 (15.8)	0 (0.0)	9 (18.8)		
3	15 (26.3)	6 (66.7)	9 (18.8)		
4	2 (3.5)	0 (0.0)	2 (4.2)		
Risk group, n (%)					
Low risk (0-2)	40 (70.2)	3 (33.3)	37 (77.1) [a]		**0.015** ǂ
High Risk (≥3)	17 (29.8)	6 (66.7) [b]	11 (22.9)		

** Mann-Whitney Test; ǂ Fisher's Exact Test; [a] Specificity; [b] Sensitivity
Abbreviation: CA – coronary artery; IQR – inter-quartile range

Discussion

The present study provides a comprehensive account of validation of Egami Score to predict IVIG resistance among children with KD in Malaysia. In this study, the prevalence of IVIG resistance was 13.6% and this was similar to the result of studies previously conducted in Japan and United States, which reported the IVIG resistance range between 13-21% (8-11).

In our study, the Egami score could predict IVIG resistance with a sensitivity of 66.7%, specificity of 77.1%, PPV of 35.3% and NPV of 92.5%. Therefore, by applying the Egami scoring system on the multi-ethnic Malaysian paediatric patients, it is predicted that 66.7% of patients with IVIG resistance will be categorised as the high-risk group while 77.1% of patients who were IVIG responders will be categorised as the low-risk group. In other words, if a patient is categorised as high risk according to the Egami score, the likelihood to develop IVIG resistant is 35.3%, whereas for those in low risk group, the likelihood to respond to IVIG would be 92.5%. If the Egami scoring system can be applied to predict IVIG resistance among the Malaysian paediatric population who has KD, it will help in planning early interventional therapies and prevent the occurrence of CA aneurysms. Previous literature has reported on the use and efficacy of single dose methylprednisolone (30mg/kg/day) in combination with IVIG (2g/kg for 1 day) plus Aspirin (30mg/kg/day) as primary treatment for those predicted to be at high risk of IVIG resistance based on Egami score. The regimen has been shown to lower the incidence of CA abnormalities and IVIG resistance (20).

The Egami Score was well established in Japan and using the Egami score of three points and above as cut off point has been shown to be 78% sensitive and 76% specific to predict IVIG resistance in the Japanese population (8). Our findings showed a similar specificity with that of the Japanese population, but with lower sensitivity. Another study conducted by Sleeper *et al.* in the North American population(18) also showed low sensitivity and moderate to high specificity. A recent study on Western Mediterranean population in Catalonia, Spain reported 26% sensitivity and 82% specificity, with the NPV of 85% and PPV of 22% (21). On the other hand, In another study based on 182 patients from US Midwest, Egami score was found to have a sensitivity of 22% and a specificity of 95% (22). An older study by Tremoulet *et al.* reported sensitivity of 33.3% and specificity of 89.3% when applied to their Asian patients(13).

The difference in the sensitivities and specificities observed in the different studies are probably due to the different definition of IVIG resistance that were used. In our study, patients were defined as having IVIG resistance based purely on the body temperature (>37.5ºC). In the Japanese population, patients were defined as having IVIG resistance if CRP did not reduce by more than 50% within 48 hours after the initial IVIG treatment (8). CRP was not included in the analysis of the current study because the measurement of CRP was not repeated after 48 hours in most of the patients. However, studies from the North America and San Diego population defined IVIG resistance as having persistent or recrudescent fever of ≥38ºC instead of ≥37.5ºC, and the reduction in CRP value was not considered (13,18). In contrast, the study by Sánchez-Manubens *et al.*, IVIG resistance is defined as patient who required a second dose of IVIG, and was not based on the rise in

body temperature (21). Thus, it would be more meaningful if future studies with standardised definition of IVIG resistance could be performed to enable direct comparison.

In this study, CA involvement was found to be higher with 31.8% compared to those reported in other studies where CA involvement were only seen in 15-20% of patients with KD (23,24). Another study done in Malaysia in 2012 also found similar results where only 28.6% of patients had CA abnormalities (25). IVIG resistance is a significant risk factor for CA aneurysms (12,13). In our study, the incidence of CA aneurysms ranged between 5.5% among IVIG responders to 50% among IVIG resistant patients. A study from Japan found that CA aneurysms ranged from 0% in IVIG responders to 29.2% in IVIG resistant patients (8). In a San Diego study, the incidence of CA aneurysms were reported as 3% in IVIG responders to 15% in IVIG resistance (26). Another study by Loomba *et al.* among Midwestern US population also found that the incidence of CA aneurysms to range between 4.8% in IVIG responder to 12% in IVIG resistant patients (22). Collectively, these results show that IVIG resistance increases the incidence of CA aneurysms, though at different rate.

According to the Japanese Ministry of Health, CA is classified as abnormal when the internal lumen diameter is more than 3mm in children younger than 5 years or more than 4 mm in children 5 years or older, when the internal diameter of any segment measures at least 1.5 times that of an adjacent segment or when the CA lumen is clearly irregular(8). Egami score was reported to have the sensitivity of 61% and specificity of 81% in predicting CA lesions in the Japanese study (8). In this study, however, we considered CA aneurysms and obtained similar sensitivity and specificity (67% and 77% respectively). Studies done by Sleeper *et al*. on the other hand, found no significant association between Egami score and CA abnormalities (18).

In the current study, patients with IVIG resistance have significantly higher level of WBC, total bilirubin, percentage of neutrophils, and lower percentage of lymphocytes. Percentage of neutrophil is a risk factor for IVIG resistance in calculating the Kobayashi Score (9) and Formosa Score (17) while increased total bilirubin is a risk factor for resistance in the Sano Score (10). A recent prospective study on the impact of neutrophil-lymphocyte ratio (NLR) in predicting the outcomes of Kawasaki disease showed that IVIG resistant patients demonstrated significantly higher NLRs in the acute febrile phase and 2 days after IVIG treatment as compared to IVIG responsive patients (27). Based on our result, this indicated that high neutrophil level could be a predictive factor for IVIG resistance. However, in view of the small number of patients with IVIG resistance in this study, regression analysis was not performed. Further studies with larger sample size should be carried out and regression analysis could be done to confirm this. A new scoring system incorporating risk factors such as WBC, neutrophil, lymphocyte, and bilirubin can be developed to obtain higher sensitivity and specificity for our population.

There are several limitations in this study. The low incidence of KD was due to partial records retrieval following the change in the record system in 2008. Due to the retrospective nature of the study, it is impossible to retrieve laboratory results on the standard days of illness (day one being day when fever start). To reduce the bias due to the day laboratory data were obtained, all the laboratory data were obtained before IVIG was given, and statistical test was done to make sure that there was no significant difference in the days the laboratory data were obtained for the IVIG resistance group and the IVIG responder group (median day 5 of illness, p= 0.995). This was because during data collection for this study, it was observed that the number of days of illness may affect the Inflammatory marker values and platelet counts. This could be explained by the changes of clinical laboratory values over the acute and subacute phases of the illness (28). The onset of thrombocytosis is common in the second week of fever (29). Another limitation of this study was that the complete laboratory data was not available for all patients which further reduced our sample size and this may also be a source of bias.

Conclusion

The validation of Egami score in the Malaysian population to predict IVIG resistance showed that the Japanese scoring system was significantly associated with IVIG resistance in our patient population. However, the Egami score was not sensitive enough to be applied as the only method for the prediction of IVIG resistance among the paediatric patients with KD. Further studies are needed to develop better predictive models for our population so that early identification of patients with the risk of IVIG resistance and CA aneurysms are possible.

Acknowledgments

We are grateful to Dr Choo Chong Ming, the Head of Paediatric Department Hospital Sultan Abdul Halim, Dr Thiyagar Nadarajaw, the Head Paediatric Department of Hospital Sultanah Bahiyah and Miss Jessica Lim Ern Sze, the Paediatric Pharmacist of Hospital Sultanah Bahiyah, for their support in this research and their help in obtaining the full patients lists and medical records of patients with Kawaski disease. We would like to thank the Director General of Health Malaysia for his permission to publish this article.

Conflict of Interest Statement

This research received no grant from any funding agency in the public, commercial or not-for-profit sectors. The Author(s) declare(s) that there is no conflict of interest

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