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Review Article

A Comprehensive Overview of Risk Scoring Systems for Predicting Intravenous Immunoglobulin (IVIG)-Resistance in Kawasaki Disease

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Abstract

It is important to predict Kawasaki Disease (KD) patients who will be resistant to Intravenous Immunoglobulin (IVIG) before starting the initial treatment, as these patients may have severe inflammation and vasculitis, which will likely lead to the development of Coronary Artery Lesions (CALs). An intensive initial treatment combined with IVIG and additional anti-inflammatory drugs is reported to reduce the occurrence of IVIG resistance and CALs. Although risk scoring systems using usual laboratory data to predict IVIG-resistant patients have mainly been developed in Japan, these systems did not accurately predict non-responders to IVIG among patients in the other countries. In this review, we provide a comprehensive overview of the main risk scoring systems and evaluate the relevant literature.

Introduction

Kawasaki Disease (KD) is an acute systemic vasculitis that mainly occurs in infants and young children [1]. Although intravenous Immunoglobulin (IVIG) is an effective treatment for KD [2], approximately 10-20% of KD patients are resistant to IVIG therapy [2,3]. IVIG-resistant patients with KD have a higher risk of developing coronary artery lesions (CALs) than responders to IVIG therapy [4,5]. It is important to predict IVIG-resistant KD patients before starting the initial treatment, because intensive initial combination therapy with IVIG and other anti-inflammatory drugs, such as Ulinastatin [6], steroid [7,8] and infliximab [9], may reduce the occurrence of IVIG resistance and/or CALs. There are several risk scoring systems for predicting IVIG resistance in KD patients; the Kobayashi [10], Egami [11] and Sano [12] risk scores have been commonly used in Japan. Recently, we reported a new risk scoring system using two blood cell subtype ratios, the neutrophil-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) [13]. Furthermore, several researchers have reported other risk scoring systems in such countries as the U.S. [14], Taiwan [15] and China [16-18]. The aim of this review is to compare the predictive validity among these risk scoring systems and assess their problems and limitations.

Risk scoring systems for predicting IVIG resistance in KD

The main risk scoring systems for predicting the IVIG resistance in KD, which have been reported to date, are summarized in Table 1. The parameters of the Egami score [11] consist of alanine aminotransferase (ALT) ≥80 IU/L (2 points), age ≤6 months (1 point), days of illness ≤4 days (1 point), C-reactive protein (CRP) ≥8 mg/dl (1 point) and platelet count ≤300×103/mm3 (1 point). In the high-risk group (score ≥3), the sensitivity and specificity in the prediction of IVIG resistance were 78% and 76%, respectively. The parameters of the Sano score [12] consist of Aspartate Amino Transferase (AST) ≥200 IU/L (1 point), CRP ≥7 mg/dl (1 point) and total bilirubin ≥0.9 mg/dl (1 point). In the high-risk group (score ≥2), the sensitivity and specificity in the prediction of IVIG resistance were 77% and 86%, respectively. The parameters of the Kobayashi score [10] consist of sodium ≤133 mmol/L (2 points), days of illness at initial treatment ≤4 days (2 points), AST ≥100 IU/L (2 points), % of neutrophils ≥80 (2 points), CRP ≥10 mg/dl (1 point), age ≤12 months (1 point) and platelet count ≤300×103/mm3 (1 point). In the high-risk group (score ≥4), the sensitivity and specificity in the prediction of IVIG resistance were 86% and

68%, respectively. Recently, Kawamura et al. reported that the combination of NLR ≥3.83 and PLR ≥150 is a useful predictor of IVIG resistance in KD [13], and the sensitivity and specificity of NLR ≥3.83 and PLR ≥150 in the prediction of IVIG resistance were 71% and 69%, respectively. These simple ratios are convenient and cost-effective in comparison to other scoring systems.

Table 1: Risk scoring systems predicting IVIG resistance in KD patients.

Nation	Scoring system	No. of KD patients enrolled	No. of IVIG -resistant patients	Risk factors	Points	High risk	Sensitivity (%)	Specificity (%)
Japan	Egami	320	41	ALT≥80 IU/L	2	≥3 points	78	76
				Age≤6 months	1			
				Illness days≤4	1			
				CRP≥8 mg/dl	1			
				PLT≤300×10^3/mm^3	1			
	Sano	112	22	AST≥200 IU/L	1	≥2 points	77	86
				CRP≥7 mg/dl	1			
				Total bilirubin ≥0.9 mg/dl	1			
	Kobayashi	528	148	Sodium<133mmol/L	2	≥4 points	86	68
				Illness days≤4	2			
				AST≥100 IU/L	2			
				% of neutrophils≥80	2			
				CRP≥10 mg/dl	1			
				Age≤12 months	1			
				PLT≤300×10^3/mm^3	1			
	Kawamura	405	85	NLR≥3.83	1	≥2 points	71	69
				PLR≥150	1			
US	San Giego	362	60	% of bands≥20	2	≥2 points	73	62
				Illness days≤4	1			
				GGT≥60 IU/L	1			
				zHgb≤-2	1			
Taiwan	Formosa	248	29	% of neutrophils≥60	2	≥3 points	86	81
				Albumin<3.5 g/dl	1			
				Positive lymphadenopaty	1			

China	Fu	1177	211	% of neutrophils≥80	2	≥4 points	54	71
				Illness days≤4	2			
				CRP≥8 mg/dl	2			
				Polymorphous exanthema	1			
				Change around the anus	1			
	Tang	910	46	age<6 months	2	≥3 points	71	76
				Albumin<3.5 g/dl	2			
				Edema of extremities	1			
				Rash	1			
				% of neutrophils≥80	1			
	Hua	2126	380	Fever duration≥7 days	2	≥4 points	61	67
				Delayed diagnosis	1			
				GGP≥25U/L	1			
				Sodium<135mmol/L	1			
				NLR≥2.8	1			
				PLT<350×10^3/mm^3	1			

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transferase; NLR, neutrophil-lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelet; zHgb, age-adjusted hemoglobin concentration.

In the US, the San Diego score [14] was proposed. The parameters consist of % of bands ≥20 (2 point), illness days≤4 (1 point), γ-glutamyl transferase (GGT) ≥60 IU/L and age-adjusted hemoglobin concentration (zHgb) ≤-2. In the high-risk group (score ≥2), the sensitivity and specificity in the prediction of IVIG resistance were 73% and 62%, respectively. In Taiwan, the Formosa score [15] was reported. The parameters consists of % of neutrophils ≥60 (2 points), albumin <3.5 g/dl (1 point) and positive lymphadenopathy (1 point). In the high-risk group (score ≥3), the sensitivity and specificity in the prediction of IVIG resistance were 86% and 81%, respectively. In China, Fu et al. reported a scoring system. The parameters consist of % of neutrophils ≥80 (2 points), illness days ≤4 (1 point), CRP ≥8 mg/dl (2 pint), polymorphous exanthema (1 point) and change around the anus (1 point) [16]. In the high-risk group (score ≥4), the sensitivity and specificity in the prediction of IVIG resistance were 54% and 71%, respectively. Tang et al. reported another scoring system. The parameters consist of age <6 months (2 points), albumin 3.5<g/dl (2 points), edema of extremities (1 point), rash (1 point) and % of neutrophils ≥80 (1 point) [17]. In the high-risk group (score ≥3), the sensitivity and specificity in the prediction of IVIG resistance were 71% and 76%, respectively. Recently, Hua et al. reported a new scoring system. The parameters consist of fever duration ≥7 days (2 points), delayed diagnosis (1 point), GGP ≥25 mg/dl (1 point), sodium <135 mmol/L (1 point), NLR ≥2.8 (1 point) and platelet count ≤350×103/mm3 (1 point) [18]. In the high-risk group (score ≥4), the sensitivity and specificity in the prediction of IVIG resistance were 61% and 67%, respectively. As described above, each of risk scoring systems are determined based on different clinical data and symptoms, although some factors are duplicated among these scoring systems.

Definition of IVIG Resistance

There are differences in the definition of IVIG resistance in each study. Egami defined IVIG resistance as persistent fever (≥37.5°C) and a fall in CRP by <50% within 48 hours after IVIG therapy [11]. Sano defined IVIG resistance as persistent fever (≥37.5°C over 24 hours) after finishing IVIG therapy [12]. Kobayashi and Kawamura defined IVIG resistance as persistent fever lasting >24 hours after the completion of the initial treatment or in the presence of recrudescent fever associated with KD symptoms after an afebrile period [10,13]. The San Diego score defined IVIG resistance as persistent fever (≥38.0°C rectally or orally) for at least 48 hours but no longer than 7 days after IVIG therapy [14]. The Formosa score defined IVIG resistance as persistent fever or development of recrudescent fever associated with KD symptoms after afebrile period [15]. Fu and Hua defined IVIG resistance as persistent or recrudescent fever at any time 48 hours to 2 weeks after IVIG therapy and at least 1 of the standard diagnostic criteria [16,18]. Tang defined IVIG resistance as recrudescent or persistent fever ≥36 hours after the end of IVIG infusion [17]. Thus, because the definition of IVIG resistance has not been standardized, international consensus will be needed in the near future. In the 2017 Kawasaki disease guidelines from the

American Heart Association, the definition of IVIG resistance was recrudescent or persistent fever at least 36 hours after the end of IVIG infusion [19].

The Application of Risk Scoring Systems to KD Patients in Different Nations

Several authors have assessed the sensitivity and specificity of risk scoring systems when they were applied to KD patients in the other countries (Table 2). The Kobayashi risk score (≥4), Egami risk score (≥3) and Sano risk score (≥2) have good specificity (87%, 85% and 85%, respectively) but low sensitivity (33%, 42% and 40%, respectively) for predicting IVIG resistance in KD patients in North America [20]. Similarly, the Kobayashi risk score (≥4), Egami risk score (≥3) and Sano risk score (≥2) have good specificity (87%, 87% and 92%, respectively) but low sensitivity (31%, 34% and 28%, respectively) for predicting IVIG resistance in KD patients in Korea [21]. In KD patients in China, Song et al. reported that the Kobayashi risk score (≥4) and Egami risk score (≥3) have good specificity (85% and 84%, respectively) but low sensitivity (16% and 14%, respectively), the San Diego risk score (≥2) has high sensitivity (95%) but very low sensitivity (3%), and the Formosa score (≥3) has relatively low specificity (47%) and sensitivity (43%) for predicting IVIG resistance [22]. Qian et al. reported that the sensitivity of Kobayashi risk score (≥4), Egami risk score (≥3), Sano risk score (≥2), Kawamura risk score (≥2) and Formosa score (≥3) were 72%, 44%, 20%, 48% and 68%, respectively, and that the specificity of these scores were 62%, 82%, 91%, 66% and 48%, respectively [23]. In the United Kingdom, the Kobayashi risk score (≥4) had relatively low sensitivity (58%) and low specificity (35%) [24]. In the Kobayashi score, a cut-off risk score of 5 points was also reported to be effective for predicting IVIG resistance in Japanese patients with KD [7,25]. The Kobayashi risk score (≥5) is reported to predict IVIG resistance in Iranian patients with KD, with 50% sensitivity and 94% specificity [26].

Table 2: Sensitivity and Specificity of risk scoring systems when applied to different ethnic group.

Nation	Authors	No. of KD patients enrolled	No. of IVIG -resistant patients	Scoring system	Sensitivity (%)	Specificity (%)
U.S.	Sleeper	71	9	Kobayashi (≥4)	33	87
		90	12	Egami (≥3)	42	85
		66	10	Sano (≥2)	40	85
Korea	Kim	703	118	Kobayashi (≥4)	31	87
				Egami (≥3)	34	87
				Sano (≥2)	28	92
China	Song	1163	63	Kobayashi (≥4)	16	85
				Egami (≥3)	14	84
				San Diego (≥2)	95	3
				Formosa (≥3)	43	47
	Qian	504	25	Kobayashi (≥4)	72	62
				Egami (≥3)	44	82
				Sano (≥2)	20	91
				Kawamura (≥2)	48	66
				Formosa (≥3)	68	48
U.K.	Davies	59	19	Kobayashi (≥4)	58	35
Iran	Nateghian	97	19	Kobayashi (≥5)	50	94
German	Jakob	301	47	Kobayashi (≥4)	43	83
				Egami (≥3)	49	76
				Sano (≥2)	28	94
Italy	Fabi	257	43	Kobayashi (≥4)	64	63
				Egami (≥3)	41	77
				Formosa (≥3)	71	45

Recently, Jakob et al. reported that the Kobayashi risk score (≥4), Egami risk score (≥3) and Sano risk score (≥2) have low sensitivity (43%, 49% and 28%, respectively), although they have relatively high specificity (83%, 76% and 94%, respectively), in German patients with KD [27]. More recently, Fabi et el. reported that the Kobayashi risk score (≥4), Egami risk score (≥3) and Formosa score (≥3) are ineffective for predicting IVIG resistance (sensitivity: 64%, 41% and 71%, respectively; specificity: 63%, 77% and 45%, respectively) in Italian children with KD [28]. Besides, the ability of NRL and PLR to predict IVIG resistance in KD was evaluated in China: the cut-off values of NLR ≥4.36 and PLR ≥162 were useful for predicting IVIG-resistance in KD [29], and NLR ≥2.51 was useful in KD patients younger than 1 year of age [30]. Although there is a slight difference in the cut-off values of Japan [13] and China [29], the effectiveness of the NLR and PLR in predicting IVIG resistance has been proven in both countries.

Problems and Limits of Risk Scoring Systems for IVIG Resistance in KD

Many of the Japanese scoring systems (Egami, Sano and Kobayashi scores) had relatively good specificity but low sensitivity when they were applied to non-Japanese KD patients. These results indicate that the use of Japanese risk scores in other countries can exclude most patients who do not require additional therapy (low-risk patients) but cannot accurately extract patients who require additional therapies (high-risk patients). For this reason, these Japanese risk scores have not been widely used outside Japan. These regional differences could be due to genetic differences or other environmental factors [31]. It is reported that the functional polymorphism and methylation of the immunoglobulin gamma Fc region receptor II-a (FCGR2A) gene might be associated with IVIG resistance in KD patients [32,33]. As there is a difference in the incidence of KD among countries, the disease severity and the effectiveness of IVIG therapy might also be different. It seems difficult to establish a universal risk scoring system for IVIG resistance in KD due to racial differences. Thus, it might be better to aim to establish discrete risk scoring systems for each country. It would be preferable if the risk score is simple and convenient. The determination of cut-off values for the NLR and PLR in each country may warrant investigation because these ratios are easily calculated. In summary, the prediction of failure to respond to IVIG therapy is important for identifying KD patients who may need additional anti-inflammatory treatments, because intensive therapy can be reduce the incidence of IVIG resistance and CAL formation. Although several risk scoring systems of IVIG resistance have been proposed, many of these failed to effectively predict IVIG resistance in other countries. Further studies will be needed to obtain consensus on a risk scoring system for predicting IVIG resistance in KD.

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