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ORIGINAL ARTICLE

Risk factors and derived formosa score for intravenous immunoglobulin unresponsiveness in Taiwanese children with Kawasaki disease

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KEYWORD
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Background/purpose: Kawasaki disease (KD) is the most common pediatric vasculitis. The study aimed to identify the risk factors of intravenous immunoglobulin (IVIG) unresponsiveness from the initial clinical parameters of the Taiwanese KD patients.
Methods: We enrolled 248 KD (development dataset: 181, validation: 67) patients who received IVIG within 10 days after fever onset. IVIG unresponsiveness was defined by persistent fever beyond 24 hours after IVIG or recrudescent fever with KD symptoms.
Results: From the development dataset (181 patients), IVIG unresponsiveness was noted in 22 patients (12.1%). The preIVIG levels of albumin, percentage of neutrophils, and positive lymphadenopathy were identified with highest risk for IVIG unresponsiveness. These three variables were used to construct a three-variable logistic regression model, which yielded an area under the receiver–operating-characteristics curve of 0.87. These three variables were further used to generate a composite scoring model (Formosa score) which yielded a sensitivity of 90.9% and specificity of 81.3% for a cut-off point of three or more. Validation in an independent cohort (67 KD patients) yielded sensitivity and specificity of 71.4% and 81.0%, respectively.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: We have established a simple three-variable Formosa score for KD patients to identify early those at risk of IVIG unresponsiveness for timely aggressive immunomodulation initially.

Introduction

Kawasaki disease (KD) is the most common pediatric systemic vasculitis. The incidence in Taiwan is the third highest globally, just lower than that in Japan and Korea.[1,2] The state-of-the-art therapy recommends the intravenous immunoglobulin (IVIG) therapy during the acute stage, which is effective to decrease the coronary complications. In untreated KD patients, coronary arterial lesions (CAL) with varying severity was noted in 15–25% of the patients.[1,2] However, 10–15% of patients may still have persistent or recurrent fevers after completion of the IVIG therapy, i.e., patients with IVIG unresponsiveness. This subgroup of KD patients is considered more risky to have CAL.[3] There are two treatment strategies for patient with IVIG unresponsiveness. One is rescue therapy with a second course of IVIG,[4] steroid,[5] infliximab,[6] or a combination of the above medication. The other is add-on therapy, i.e., administration of IVIG and steroid to certain KD patients who are considered high risk for being IVIG nonresponders by using a scoring system, such as the Kobayashi scoring system.[3,7–9] However, regional or population differences in such risk scoring systems are possible and the efficacy needs to be validated. For example, when we applied the Kobayashi score to the KD patients in Taiwan,[10] we found that the sensitivity and specificity to predict IVIG unresponsiveness was only 62% and 71%, respectively. Therefore, this study aimed to identify the risk factors from the clinical and laboratory parameters of our cohort and to construct a novel risk scoring system (Formosa score) for an early detection of the KD patients with IVIG unresponsiveness.

Materials and methods

The study was approved by National Taiwan University Hospital Institutional Research Board (NTUHREC-201411077 RIN).

Patients

We enrolled patients with KD who had at least five of the following six manifestations[1,11]: fever for $>$ 5 days, skin rash, neck lymphadenopathy, nonpurulent bulbar conjunctivitis, red lip with fissure and/or strawberry tongue, and palm/sole erythema and induration followed by desquamation. We also enrolled patients with incomplete KD, defined as occurring in patients who had less than five of the above manifestations but who had a coronary arterial abnormality. Those KD patients who were admitted to our institution (development dataset: between January 2009 and December 2012; validation dataset: between January 2013 and June 2014) and administered IVIG (2 g/Kg $\times$ 1 day or 1 g/Kg $\times$ 2 days) within 10 days after fever onset were enrolled as development dataset. The 1st day of the illness was defined as the day of fever onset. Patients were considered afebrile when their body temperature at the axilla remained $<$ 37.5°C for $>$ 24 hours. The dose of aspirin was decreased to 5 mg/kg/d after fever subsided. Medical records were reviewed and the details of the manifestations, including the six principal symptoms, i.e., fever, polymorphous exanthema, changes in extremities (erythema, edema, and peeling), bulbar conjunctivitis, changes of lips and oral cavity (red lip, strawberry tongue, and injection of oral mucosa), and cervical lymphadenopathy, as well as the erythematous changes at Bacillus Calmette-Guérin (BCG) inoculation site were collected. Laboratory data including blood cell count, urinary analysis, levels of albumin and aspartate aminotransferase, and acute phase reactants during the acute phase were obtained. All children received echocardiography during the febrile stage and the subacute phase (1 week, 3 weeks, 6 weeks, and 3 months after fever onset, and the subsequent frequency varied depending on the severity of the CAL).

IVIG unresponsiveness was defined if, after the completion of the first course of IVIG, patients had fever persistent for $>$ 24 hours or developed recrudescent fever associated with KD symptoms after an afebrile period.[1,4,11] From January of 2013 to June of 2014, a validation dataset of additional 67 KD patients were studied prospectively to test the accuracy of prediction.

Coronary arterial abnormalities were defined whenever body surface area-adjusted z-score of any coronary vessels[12] was $\geq +2.5$, including left main coronary artery, left anterior descending artery, and right coronary artery.

Statistical analysis

We performed analyses using SPSS version 18 (SPSS Inc., Chicago, IL, USA). The data were expressed as mean $\pm$ standard deviation (medians with ranges), and percentages for categorical data we used Student *t* test for comparisons of numerical data. The Chi-square test was used to compare categorical data. Variables related to refractory events with $p < 0.1$ in the univariate analysis were entered into the multivariate model. Multivariate logistic regression model was conducted to evaluate the association of multiple risk factors with IVIG unresponsiveness. Results are expressed as a hazard ratio with a 95% confidence interval (CI). Statistical significance was set at $p < 0.05$.