Title: Epidemiologic Features of Kawasaki Disease in Shanghai From 2013 Through 2017

Document type: Study Protocol and Statistical Analysis Plan

Date: March 7, 2019

Study Protocol

Data Collection

This study was conducted based on the former three surveys of KD in Shanghai. A set of questionnaires and diagnostic guidelines were sent to 50 hospitals providing pediatric medical care in Shanghai. All patients discharged from these hospitals from January 1, 2013 through December 31, 2017 with an International Classification of Diseases (ICD) code for KD or mucocutaneous lymph node syndrome (ICD9 446.1 and ICD10 M30.3) were enrolled in the study. Data were collected by pediatricians, including demographic information, clinical manifestations, prognosis, laboratory indexes, treatment, and echocardiographic findings. The contents of the questionnaire was mildly modified with addition of erythema and induration at Bacillus Calmette-Guérin (BCG) sites, the date of appearance and disappearance of CAL measured by echocardiography, the sites and severity of valvular regurgitation, the presence of coronary stenosis and coronary thrombosis, and some new laboratory indexes including neutrophil count (NEUT), lymphocyte count (LYM), aspartate transaminase (AST), serum sodium (Na), and total bilirubin (TB).

Inclusion and Exclusion Criteria

After all questionnaires were returned, two senior pediatric cardiologists were responsible for further verification. Patients who met the diagnostic criteria for KD released by the American Heart Association (AHA)[1,12] were included in this study. Exclusion criteria were as follows: 1) not meeting the above diagnostic criteria; 2) not in acute phase; 3) repeated cases; 4) cases not from 2013 to 2017. All eligible cases were entered into to the KD database.

Definitions

Among patients diagnosed with KD, those with persistent fever and at least 4 of 5 principal features were classified as complete KD (CKD). The others with persistent fever but less than 4 principal features were classified as incomplete KD (IKD).

The first day of illness was defined as the first day of fever. Intravenous immunoglobulin (IVIG) resistance was defined as persistent fever (>38°C) after 36 hours of completion of initial IVIG infusion or recurrent fever requiring another dose of IVIG or other adjunctive therapies.

Laboratory indices before initial IVIG infusion were recorded, including the highest values of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count (PLT), white blood cell count (WBC), creatine kinase-muscle/brain (CK-MB), alanine aminotransferase (ALT), AST, and TB, and the lowest values of hemoglobin (HB), serum albumin (ALB), and Na if laboratory tests were performed more than once before initial IVIG. NEUT and LYM of the same blood test with highest WBC were also recorded.

On two-dimensional echocardiography, a coronary artery was defined as abnormal if the luminal diameter was >3.0 mm in children aged younger than 5 years or >4.0 mm in those aged 5 years and older, or when the internal diameter of a segment was ≥1.5 times that of an adjacent segment[13]. A medium aneurysm was defined as an internal luminal diameter from 4 to 8 mm and a giant aneurysm was defined as an internal luminal diameter >8 mm. The coronary measurements of the most severe echocardiography were recorded if the measurement was performed more than once. Coronary stenosis was assessed only by coronary angiography and coronary artery thrombosis was assessed by echocardiography or angiography.

Long-term outcomes of CAL were classified into three categories based on the duration of the lesions from the appearance of CAL detected by echocardiography, including resolution within one month, resolution after one month, and sustained lesions. All patients without echocardiography suggesting resolution of CAL during the 5-year period were classified as the sustained lesions group, regardless of spans of the follow-up time. Resolution was defined as regression of CAL to normal.

Statistical Analysis

The incidence of KD was calculated by dividing the number of newly diagnosed KD patients under 5 years old who inhabited in shanghai by the resident population of the corresponding age group in Shanghai. Census data were acquired from Shanghai Municipal Center for Disease Control and Prevention.

Data are presented as mean (±standard deviation) or median (interquartile range) for continuous variables, and count (percentage) for categorical variables. Continuous variables were compared between groups by using unpaired Student's t tests or Mann-Whitney U test. Categorical variables were compared by using χ^2 test or Fisher exact test.

Univariate analysis was performed to explore potential risk factors for CAL using above statistical methods, including age of onset, male sex, KD type, fever days before initial IVIG, the dose of initial IVIG and all 13 laboratory indexes. Among them, CRP was divided into four groups based on quartiles due to the presence of truncated values. Multivariate logistic regressions were performed to identify risk factors independently associated with CAL. A two-tailed P<0.05 was considered statistically significant. Analyses were performed with SPSS 23.0 (IBM, Armonk, NY).

A Kaplan-Meier curve was drawn to describe the resolution time of CAL and the Log-rank test was performed for comparison between groups. Event was defined as regression of CAL to normal. Time was defined as months from the appearance of CAL to an event by echocardiography, or to last echocardiography if no event occurred. Patients who did not have an event or lost contact during the 5-year period (from 2013 to 2017) were considered as censored.