Journal of Microbiology, Immunology and Infection (2018) 51, 184—190

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Characteristics of children with Kawasaki disease requiring intensive care: 10 years' experience at a tertiary pediatric hospital

Ching-Chia Kuo [a], Yu-Shin Lee [a], Ming-Ru Lin, Shao-Hsuan Hsia, Chih-Jung Chen, Cheng-Hsun Chiu, Mao-Sheng Hwang*, Yhu-Chering Huang*

Department of Pediatrics, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

Received 4 March 2016; received in revised form 25 May 2016; accepted 27 June 2016
Available online 29 July 2016

KEYWORDS
intensive care;
Kawasaki disease;
Kawasaki disease shock syndrome;
shock;
Taiwan

Abstract *Background/Purpose:* Kawasaki disease (KD) is a febrile systemic vasculitis, and some patients may develop serious complications requiring intensive care. We aim to ascertain the clinical presentations and outcomes of these patients.
Methods: From October 2004 to October 2014, children with KD who had stayed in the pediatric intensive care unit (ICU) for acute stage treatment were defined as case patients; for each case, three age/sex-matched patients with KD but without ICU stay, if identified, were selected as control patients. Clinical data were retrospectively collected and analyzed.
Results: Among the total of 1065 KD patients, we identified 26 case patients and 71 controls for statistical analysis. ICU patients had a longer fever duration, and tended to have hemoglobin level < 10 g/dL, platelet count $< 150 \times 10^9$/L, band cell percentage $> 10\%$, peak serum C-reactive protein level > 200 mg/L, serum albumin value < 3 g/dL, and often presented with multiorgan system involvement. Time from symptom onset to the diagnosis of KD was similar between the two groups, but ICU patients were less likely to have KD as a leading admission diagnosis. Shock (73.1%, $n = 19$) was the most common reason for ICU admission. ICU patients were more likely to receive antibiotics, albumin infusion, and require a second dose of intravenous immunoglobulin or steroid therapy. No in-hospital mortality was observed.

* Corresponding authors. Department of Pediatrics, Chang Gung Children's Hospital and Chang Gung Memorial Hospital, Number 5, Fuxing Street, Guishan District, Taoyuan City 333, Taiwan.
E-mail addresses: hms3013@cgmh.org.tw (M.-S. Hwang), ychuang@cgmh.org.tw (Y.-C. Huang).
[a] These two authors equally contributed to this manuscript.

http://dx.doi.org/10.1016/j.jmii.2016.06.004

Conclusion: Patients with KD requiring ICU admission are significantly associated with multi-organ involvement, abnormal hematological and biochemistry biomarkers, KD recognition difficulty at the time of admission, and intravenous immunoglobulin-refractory KD.

Introduction

Kawasaki disease (KD) is an acute febrile vasculitis that mainly affects medium-sized vessels at the systemic level; its etiology remains unclear. Intravenous immunoglobulin (IVIG) and aspirin are the treatment of choice to lower the risk of coronary artery lesion (CAL) formation. If left untreated, KD may result in coronary artery aneurysms in 15–25% of patients,[1] and, although rarely, might further develop into fatal myocardial infarction. The reported case-fatality rate is low,[2] and most deaths occur within 1–2 months of onset.[3,4] Several studies have reported the features of KD shock syndrome (KDSS) over the past few years in North America and Taiwan,[5–8] which included difficulty for early recognition, delay of treatment, and increased need for IVIG retreatment. In addition to KDSS, we encountered a group of children with KD who did not develop hemodynamic instability in the acute stage but still required intensive care in the critical care settings. Therefore, we conducted a case–control study to delineate the characteristics of children with KD requiring intensive care.

Methods

Hospitalized pediatric patients with Kawasaki disease were selected by discharge code in charts (International Classification of Diseases, 9th Revision, Clinical Modification code 446.1) from October 1, 2004 to October 1, 2014 at the Chang Gung Children's Hospital, Linkou, Taiwan. Demographic data and clinical characteristics were collected via retrospective electronic medical records reviewed independently by two pediatric infectious disease specialists.

Those who had been admitted to the intensive care unit (ICU) during their hospital stay were categorized as ICU case patients. Patients were excluded if any of the following conditions was met: underlying primary immunodeficiency diseases receiving immunoglobulin therapy; conditions requiring systemic corticosteroid administration for more than 4 weeks; evidence of bacterial growth from sterile sites; concomitant illness with a diagnosis other than Kawasaki disease during the same hospitalization; or ICU admission resulting from conditions other than the acute, direct impacts of Kawasaki disease. Conditions requiring ICU admission were categorized by the Guidelines for Developing Admission and Discharge Policies for the Pediatric Intensive Care Unit. Controls were selected from patients who had a discharge diagnosis of Kawasaki disease but were not admitted to the ICU. Three control patients, if achievable, were identified for each case patient matched by sex and age (within 3 months of range).

Electronic medical records of enrolled ICU cases and control patients were reviewed retrospectively to collect the following data: demographic data (age, sex, admission season, and days of fever prior to admission); laboratory test results (white blood cell count, hemoglobin, platelet count, percentage of neutrophil, percentage and count of band cell, C-reactive protein, aspartate aminotransferase, alanine transaminase, blood urea nitrogen, creatinine, and albumin); clinical information (overall duration of fever, days of hospitalization, tentative diagnosis at presentation, time to documented diagnosis of Kawasaki disease, and time to IVIG therapy); treatments (empiric antibiotics, aspirin, IVIG, adjuvant corticosteroids, albumin transfusion, and inotropic agents), and echocardiogram findings (measurements of coronary artery lesions and time to recovery from coronary artery lesions). The day of fever onset was defined as Day 0. Spring months were defined as February–April, summer months were defined as May–July, and so on. Diagnosis of complete or incomplete Kawasaki disease was classified based on the published standard clinical criteria. Measurements of CALs were performed by pediatric cardiologists according to the standard of the Japanese Ministry of Health criteria. Acute stage was defined as 0–10 days after disease onset, subacute stage as 11–21 days, convalescent stage as 22–90 days, and chronic stage as 91–365 days. For patients admitted after July 2014 and who were applied with Z-score calculation according to the department policy, we retrospectively reassessed CALs based on documented coronary artery diameter measurements of the time because the height records for Z-score calculation were not documented in some of the earlier patients.

We conducted Student *t* tests to compare means of continuous variables and Chi-square analysis for proportional differences. Mann–Whitney *U* test was used for comparing medians in skewed continuous variables. Data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant. This retrospective study was approved by the Institutional Review Board of Chang Gung Medical Foundation, Taoyuan, Taiwan (reference number: 103-5514B).

Results

During a 10-year period from October 1, 2004 to October 1, 2014, a total of 1065 patients were admitted to the Linkou Chang Gung Children's Hospital with a discharge diagnosis of Kawasaki disease, and 30 (2.82%) of these patients had been admitted to the ICU. The annual rate of hospitalized KD patient requiring intensive care in these 10 study years (defined from October to September of the next year) ranged from 0.93% to 4.44%.

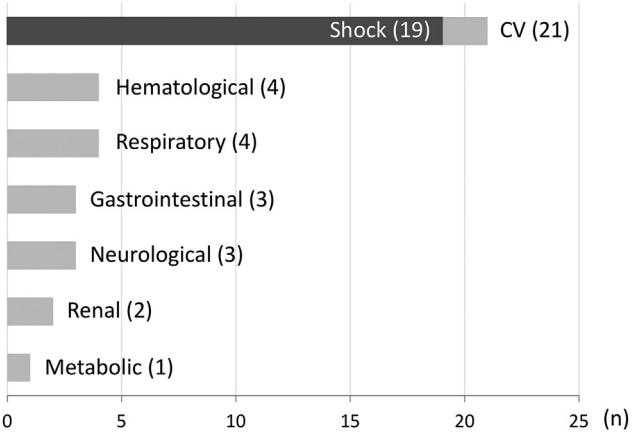

Figure 1. Events requiring intensive care unit admission categorized by organ-system. One patient may have presented with multiorgan system involvement, so the total event number was greater than the number of intensive care unit patients. CV = cardiovascular.

All 30 patients with the conditions requiring ICU admission in this study were system-wise categorized and demonstrated in Fig. 1. Nineteen of the 21 patients with cardiovascular insults had documented shock (78.9%, 15/19) or clinical symptoms/signs of impending shock identified by close monitoring of blood pressure (21.1%, 4/19), and these 19 patients were defined as KDSS patients. One patient experienced an episode of supraventricular tachycardia, and another one received pericardiocentesis. Two of the four patients with respiratory insults were intubated and put on mechanical ventilation for 3 days and 7 days, respectively. One of the two patients who developed acute renal failure required acute hemodialysis. One of the three patients with gastrointestinal involvement presented with severe ileus and suspected acute abdomen. Three of the four patients with hematologic presentations had severe anemia, hence the consequent compromised respiratory or hemodynamic status. The other developed disseminated intravascular coagulation.

After excluding four ICU patients requiring intensive care as a result of either the indirect impacts of KD or complications beyond the acute stage, we identified the remaining 26 ICU patients as case subjects for subsequent analysis, and 71 corresponding age- and sex-matched patients without ICU stay were randomly selected as controls.

Demographics

The demographic characteristics of the case and control patients are shown in Table 1. Half of the ICU patients were male, and 42% were aged < 1 year. The incidence of both ICU (34.6%, 9/26) and controls (35.2%, 25/71) was higher during the summer months. Seven (26.9%) of the 26 ICU patients were transferred from other medical facilities due to deteriorated conditions. Four of the seven transferred patients were admitted to the ICU immediately, while the other three patients were admitted to the ordinary ward first. By contrast, only one (5.3%) of the other 19 non-transfer ICU patients was directly admitted to the ICU at the first encounter with our own emergency department.

Table 1 Demographics of intensive care unit (ICU) patients and control patients.

Demographics	ICU (n = 26)	Control (n = 71)	p
Male sex (%)	50.0	52.1	0.854
Age (mo)			
Mean ± SD	32.4 ± 32.1	30.8 ± 30.4	0.819
Median (range)	22 (2–115)	21 (2–115)	0.945
< 12 mo (%)	42.3	35.2	0.522
> 60 mo (%)	15.4	15.5	> 0.999
Seasonality (%)			0.768
Spring	30.8	21.1	
Summer	34.6	35.2	
Autumn	23.1	28.2	
Winter	11.5	15.5	

Table 2 Comparison of clinical characteristics between intensive care unit (ICU) patients and control patients.

Characteristics	ICU (n = 26)	Control (n = 71)	p
Fever duration prior to admission (d)	3.8 ± 1.6	4.5 ± 2.1	0.065
Median (range)	4 (1–9)	4 (1–10)	0.153
KD as initial diagnosis (%)	42.3	66.2	0.034
Complete KD (%)	53.8	73.2	0.070
Time from fever onset to diagnosis (d)	7.0 ± 3.4	7.0 ± 2.4	0.945
Median (range)	5.5 (4–17)	6 (4–17)	0.289
> 10 d (%)	15.4	5.6	0.204
IVIG administration (%)	92.3	95.8	0.608
Time from fever onset to IVIG usage (d)	6.1 ± 2.0	6.8 ± 2.1	0.147
Median (range)	5 (4–11)	6 (4–15)	0.072
>10 d (%)	4.2	4.4	> 0.999
Time from admission to IVIG usage (d)	2.2 ± 1.9	2.4 ± 2.0	0.734
Median (range)	2 (0–8)	2 (0–9)	0.820
Repeated IVIG usage (%)	37.5	2.9	< 0.001
Aspirin usage (%)	88.5	100.0	0.018
Adjuvant steroid usage (%)	11.5	1.4	0.058
Antibiotics (%)	92.3	62.0	0.004
Inotropic agents (%)	38.5	0.0	< 0.001
Albumin infusion (%)	34.6	0.0	< 0.001
Virus isolation performed (%)	76.9	39.4	0.001
Positive for isolation (%)	5.0	21.4	0.214

IVIG = intravenous immunoglobulin; KD = Kawasaki disease.

Clinical characteristics

Detailed clinical characteristics are shown in Table 2. Both case group and control group presented a similar duration of fever at the time of admission. All of the 97 enrolled patients experienced KD for the first time. Most patients

had complete KD, and the proportion was higher in the controls. However, ICU patients were less likely to have KD as a leading diagnosis at admission than control patients (42.3% vs. 66.2%, $p = 0.03$). Twelve (46.2%) ICU patients had KD as one of the tentative diagnoses before transfer, and two of them developed the impression of KD at the time of ICU transfer. Two of the three ICU patients with suspected toxic shock syndrome or severe sepsis received IVIG therapy before the diagnosis of KD was established. Therapy with IVIG was administered in a timely manner in both groups, but ICU cases tended to need a second dose of IVIG as a result of refractory KD (37.5% vs. 2.9%, $p < 0.001$), and even adjuvant steroid treatment. Two (7.7%) of the ICU cases and three (4.2%) of the control patients did not receive IVIG therapy, and the median duration from fever onset to KD diagnosis of these five patients was 15 days (range, 9—17 days). Aspirin was not given to three (11.5%) ICU cases because of prolonged coagulopathy and anemia. The majority of hospitalized patients were prescribed with antibiotics on admission, especially the ICU group (92.3% vs. 62.0%, $p = 0.004$). One-third of ICU patients were administered with albumin supplementations. Inotropic agents including dopamine, dobutamine, milrinone, or epinephrine were applied alone (80.0%, 8/10) or in combination to 10 of the 19 shock patients, at the discretion of clinical physicians.

Table 3 Comparison of laboratory data between intensive care unit (ICU) patients and control patients.

Laboratory values	ICU ($n = 26$)	Control ($n = 71$)	p
WBC count, 10^9/L, on admission	14.7 ± 7.2	14.8 ± 6.0	0.949
WBC count, 10^9/L, peak	20.6 ± 6.9	16.60 ± 5.9	0.060
$> 20 \times 10^9$/L (%)	46.2	25.4	0.050
Hemoglobin, on admission	10.9 ± 1.8	11.3 ± 0.9	0.311
< 10 g/dL (%)	26.9	9.9	0.050
Hemoglobin, nadir, g/dL	8.6 ± 1.4	10.5 ± 1.3	< 0.001
Decrease after admission (%)	92.3	52.1	< 0.001
< 8 g/dL (%)	34.6	2.8	< 0.001
Platelet, 10^9/L, on admission	241.0 ± 167.4	378.7 ± 143.8	< 0.001
$< 150 \times 10^3$/L (%)	26.9	1.4	< 0.001
150—400 $\times 10^9$/L (%)	61.5	68.6	0.516
$> 400 \times 10^9$/L (%)	11.5	30.0	0.063
Decrease after admission (%)	76.9	15.9	< 0.001
Decrease to $< 150 \times 10^{9/}$L (%)	65.0	0.0	0.006
Platelet, $10^{9/}$L, nadir	167.7 ± 145.8	374.0 ± 141.5	< 0.001
$< 100 \times 10^{9/}$L (%)	38.5	1.4	< 0.001
Platelet, $10^{9/}$L, peak	528.3 ± 191.9	479.2 ± 175.1	0.237
Segment, %	65.4 ± 17.5	63.5 ± 14.5	0.593
Band, %, on admission	9.0 ± 11.8	1.2 ± 2.1	0.002
> 10 (%)	23.1	0.0	< 0.001
Band, count, on admission	1152.1 ± 1559.2	168.2 ± 345.5	0.004
> 700 absolute count (%)	42.3	8.6	< 0.001
Band, %, peak	15.1 ± 16.6	1.6 ± 2.1	< 0.001
> 10 (%)	50.0	0.0	< 0.001
Band, count, peak	2532.5 ± 3151.6	233.3 ± 374.7	0.001
> 700 absolute count (%)	65.4	10.0	< 0.001
CRP, mg/L, on admission	162.9 ± 87.0	111.5 ± 80.9	0.008
> 100 mg/L (%)	80.8	48.6	0.005
CRP, mg/L, peak	201.8 ± 98.2	134.0 ± 85.2	0.001
> 200 mg/L (%)	50.0	22.9	0.010
AST, IU/L, on admission	56.9 ± 43.1	59.7 ± 73.2	0.860
ALT, IU/L, on admission	65.5 ± 55.3	76.4 ± 91.0	0.580
BUN, mg/dL, on admission	20.5 ± 17.1	8.7 ± 5.1	0.002
Creatinine, mg/dL, on admission	0.6 ± 0.4	0.4 ± 0.2	0.003
> 1 mg/dL, on admission (%)	16.0	0.0	0.020
Albumin, g/dL, on admission	2.9 ± 0.5	3.6 ± 0.6	< 0.001
< 3 g/dL, on admission (%)	60.9	13.0	0.001
Albumin, g/dL, nadir	2.8 ± 0.6	3.6 ± 0.6	< 0.001
< 2.5 g/dL, nadir (%)	39.1	4.3	0.004
Albumin infusion (%)	34.6	0.0	< 0.001
Pyuria (%)	28.0	33.3	0.635

ALT = alanine transaminase; AST = aspartate transaminase; BUN = blood urea nitrogen; CRP = C-reactive protein; WBC = white blood cell.

Laboratory results

Detailed laboratory values are shown in Table 3. Patients admitted to the ICU had lower platelet counts ($p < 0.001$), higher band cell percentage ($p = 0.002$) and counts ($p = 0.004$), higher C-reactive protein (CRP) levels ($p = 0.008$), higher blood urea nitrogen ($p = 0.002$) and creatinine ($p = 0.003$) levels, and lower albumin levels ($p < 0.001$) at admission. The majority of both case and control patients had normal platelet counts at the time of admission. By comparison, initial thrombocytopenia was disclosed in seven (26.9%) ICU patients, but only one (1.4%) of the control patients. At extreme values throughout the hospital stay, the ICU patients were more likely to have lower nadir hemoglobin levels ($p < 0.001$), lower nadir platelet counts ($p < 0.001$), greater peak band cell percentage ($p < 0.001$) and counts ($p = 0.001$), higher peak CRP levels ($p = 0.001$), and lower nadir albumin levels ($p < 0.001$). Decrease of hemoglobin levels along the course of KD was significantly more common in the case patients (92.3% vs. 52.1%, $p < 0.001$). Similar decrease in platelet counts was noticed in the ICU group and reached statistical significance (76.9% vs. 15.9, $p < 0.001$). Virus isolation was performed on 28 (39.4%, 28/71) control patients and turned out positive in six of them (cytomegalovirus, enterovirus, herpes simplex virus type 1, parainfluenza virus type 1, and two patients with adenovirus, respectively), while only one out of 20 (76.9%, 20/26) tested ICU patient was positive for enterovirus.

Table 4 Comparison of clinical outcomes between intensive care unit (ICU) patients and control patients.

Outcomes	ICU ($n = 26$)	Control ($n = 71$)	p
Fever			
Duration (d)	10.2 ± 6.4	7.1 ± 2.1	0.023
Median (range)	8 (5–31)	7 (4–16)	0.061
Length of stay (d)	12.1 ± 6.5	5.7 ± 2.3	< 0.001
Median (range)	10 (4–29)	5 (2–12)	< 0.001
Overall CAL occurrence (%)	53.8	35.2	0.097
LMCA (%)	50.0	32.9	0.123
LADA (%)	31.8	26.5	0.647
RMCA (%)	34.6	19.7	0.127
Acute stage (%)	44.0	32.9	0.318
Subacute stage (%)	64.3	27.3	0.066
Convalescent stage (%)	25.0	28.1	0.791
Chronic stage (%)	16.7	15.6	> 0.999
Time for CAL normalization, ongoing CAL excluded (mo)			
Median (range)	2 (1–27)	4.5 (1–23)	0.194
Recurrent KD after discharge (%)	3.9	2.8	> 0.999
In-hospital mortality (%)	0.0	0.0	> 0.999

CAL = coronary artery lesion; KD: Kawasaki disease; LADA = left anterior descending artery; LMCA = left main coronary artery; RMCA = right main coronary artery.

Outcomes

Details of clinical outcomes are shown in Table 4. The patients admitted to the ICU needed a median of 5 more days for hospitalization ($p < 0.001$), and spent a median of 4.5 days (range, 1–9 days) in the ICU. The proportion of ICU patients developing CAL appeared to be greater than that of the control patients, but did not reach statistical significance. Five patients had ongoing coronary artery dilatation by January 1, 2015 based on their latest echocardiogram results. These patients kept follow-up visits as instructed at our cardiology outpatient clinic, and all five patients continued daily low dose aspirin administration. Based on the latest echocardiogram measurements, two ICU cases had persistent CAL for at least 60 (with aneurysm formation, 7.1 mm in diameter) and 120 months, and three control patients still had CALs at the 8th, 16th, and 102nd (with aneurysm formation, 8.3 mm in diameter) months respectively after hospitalization for KD. There was no in-hospital mortality or death from KD after discharge. Three (3.1%) patients had experienced recurrent KD by January 2015, including one patient (3.9%) from the ICU group and two patients (2.8%) from the control group.

Discussion

As the concept of KDSS has become more familiar to pediatricians in the past few years, the reported incidence rate of KDSS ranges from 2.60% to 6.95% for children in Western countries.[5–7] In this study, 2.44% (26/1065) of the KD patients required intensive care after four ambiguous cases were excluded. Composing the overall ICU admission rate, the incidence of KDSS was 1.78 per 100 KD cases during the decade we reviewed. A case–control study conducted by Chen et al[8] demonstrated the KDSS rate to be 1.9% among Taiwanese children with KD, which was similar to our results. In addition, a large-scaled population-based epidemiological report in Taiwan also revealed a lower incidence rate at 1.45%,[9] which suggested possible interracial differences regarding the development of KDSS. However, while the absence of the Asian KDSS patient in the study by Kanegaye et al[6] seemed to support the hypothetical difference in ethnicity, a higher incidence rate was not discovered in the Hispanic population by Gámez-González et al[7] in their study of Mexican children. Further analysis would be needed to clarify the association between ethnicity and KDSS.

Based on previous epidemiology reports,[10,11] KD occurs in Taiwan most frequently in the summer and least frequently in the winter. This pattern of distribution was compatible with the control patients, ICU cases, and those who developed KDSS in this study. In search of possible disease-causing infectious agents, virus isolation was performed in 76.9% (20/26) of the ICU cases in this study; nevertheless, the positive virus isolation rate was low (5.00%, 1/20). By contrast, the control patients had a higher positive isolation rate (21.40%, 6/28) although statistical significance was not reached. Several viruses were supposed to be associated with KD in Taiwan,[12] but our results did not show a similar picture in either ICU or control groups. Whether the virus isolated in this study

contributed to KD or colonized as a bystander remains uncertain. Because the virus isolation was applied only in a smaller proportion (39.4%, 28/71) of the control group at the clinicians' discretion, the detection rate and the diversity of viruses identified may not be representative of the general KD population not requiring intensive care. By contrast, the low positive rate despite more sampling might suggest a different etiology for patients with more severe KD. The detection of virus in KD patients admitted to the ICU should be interpreted with caution, and the correlation between virus infection and ICU admission warrants further investigations on a larger scale.

Our 26 ICU patients tended to have alterations in band cell values, hemoglobin levels, platelet levels, albumin levels, CRP levels, and resistance to IVIG therapy, which is consistent with previous reports.[5–8] KD patients with ICU admission generally showed significantly lower platelet levels at both admission and nadir value in the study by Dominguez et al,[5] which was echoed by Chen et al[8] showing lower initial platelet levels in shock patients. This finding was of particular interest to us because our ICU patients were not only more likely to have lower platelet values but also had a tendency to experience a decline in platelet counts after admission ($p < 0.001$). Furthermore, the ICU patients with a decline in platelet counts tended to reach a level of thrombocytopenia $< 150 \times 10^9$/L compared with control patients (65.0% vs. 0%, $p = 0.006$). Regarding ICU patients without hypotension, a similar decline occurred in 57.1% (4/7) of them, and all of the four patients went on reaching a level of thrombocytopenia $< 150 \times 10^9$/L. Thrombocytopenia in the acute stage has received attention over recent years, whereas thrombocytosis was thought to be a feature of later phase.[1] Even though the mechanism remains unclear, early thrombocytopenia is recognized as a risk factor of coronary aneurysm formation,[1,13] and possibly, for KDSS as well.[8] However, the association between thrombocytopenia and ICU patient without KDSS needs additional corroboration.

In addition, it seemed that our ICU patients were more likely to have compromised renal function. Similar to our findings, Gatterre et al[14] reported renal dysfunction in the majority of KD patients (10/11) admitted to the ICU. Several other organ systems including cardiovascular, respiratory, neurological, and gastrointestinal were also involved, and eight (72.7%) of their patients had multiple organ dysfunction syndrome. We also observed several of our cases with organ dysfunctions other than shock that urged intensive care, although hemodynamic instability remained the main reason for ICU admission in this study. A 20-month-old boy in this study presented with KD and simultaneous hemophagocytic lymphohistiocytosis (HLH) was transferred to the ICU due to altered consciousness. To our knowledge, cases with KD and subsequent HLH have scarcely been documented in the English literature.[15,16] Different from our case, Kang et al[16] reported 12 patients who developed HLH at a median of 12 days following the initial KD episode. Owing to the overlapping symptoms between KD and HLH, serial echocardiogram was crucial for differentiation and diagnosis especially when the two diseases occurred together.[15] In view of the fact that the KDSS incidence rate appeared to be lower in Taiwan compared with that in Western countries, other rare manifestations as a result of more severe inflammation required constant vigilance.

For the four ICU patients excluded for further statistical analysis, their unusual clinical presentations deserve further descriptions and may alert clinicians of the additional possible serious complications of KD. The first patient was a 6-month-old girl who presented symptoms of bronchiolitis without fever on admission, and cardiomegaly was incidentally disclosed on chest radiography. Following echocardiogram revealed massive pericardial effusion with coronary artery dilatation. Complication resulting from undiagnosed KD 5 weeks earlier was highly suspected, and the patient was transferred to ICU for pericardiocentesis. The second patient was a 38-month-old boy experiencing acute hemolysis 3 days after a second high dose IVIG therapy for refractory KD, which accounted for the rapid decrease of hemoglobin level from 11.7 g/dL to 4.5 g/dL. Methylprednisolone pulse therapy was applied and followed by 7 days of oral prednisolone. The third patient was a 4-month-old boy suspected to have Reye syndrome after high dose aspirin therapy with presentations of persistent vomiting, encephalopathy, and liver function impairments; although Reye syndrome was not confirmed since his parents did not agree to a diagnostic tissue biopsy. The fourth patient was an 8-month-old girl with incomplete KD, who developed rhabdomyolysis possibly associated with concomitant norovirus infection. This patient underwent continuous venovenous hemofiltration for 10 days, and aspirin was discontinued after normalization of dilated coronary artery 4 weeks later.

There were several limitations of this study. Firstly, the concept of KDSS was not well known in the first few years of our study period, and KDSS patients might have been misdiagnosed as toxic shock syndrome,[17,18] leading to misclassification. In order to prevent missed cases of KDSS, we retrospectively reviewed the electronic medical records of all the other patients with a diagnosis code of shock included in their discharge records, and none of these shock patients met the criteria of KD. Secondly, our study was conducted in a tertiary pediatric hospital in northern Taiwan; the findings of our cases may not be generalized to patients of other ethnicities. However, with the third highest incidence of KD worldwide,[11] Taiwan should be considered a credible representative for Asian countries until publication of new evidence. Thirdly, the case number of our ICU patients without KDSS was small, and may not have enough power to be demonstrative for its uniqueness. Multicenter, international, prospective studies may be needed to exhibit a more complete spectrum of this subgroup.

In conclusion, KDSS predominated the KD patients requiring ICU admission, but the incidence rate of KDSS in Taiwan was lower than that of Western countries. A minority of KD patients without hemodynamic instability may also require intensive care, but clinical presentations varied. It is important for pediatricians to stay aware of these more severe forms of KD for early recognition and timely treatment.

Conflicts of interest

All authors have no conflicts of interest to declare.

References

1. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;**110**:2747—71.
2. Chang RK. Hospitalizations for Kawasaki disease among children in the United States, 1988—1997. *Pediatrics* 2002;**109**:e87.
3. Nakamura Y, Yanagawa H, Kawasaki T. Mortality among children with Kawasaki disease in Japan. *N Engl J Med* 1992;**326**:1246—9.
4. Burns JC, Glode MP, Clarke SH, Wiggins Jr JW, Hathaway WE. Coagulopathy and platelet activation in Kawasaki syndrome: identification of patients at high risk for development of coronary artery aneurysms. *J Pediatr* 1984;**105**:206—11.
5. Dominguez SR, Friedman K, Seewald R, Anderson MS, Willis L, Glodé MP. Kawasaki disease in a pediatric intensive care unit: a case-control study. *Pediatrics* 2008;**122**:e786—90.
6. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009;**123**:e783—9.
7. Gámez-González LB, Murata C, Muñoz-Ramírez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. *Eur J Pediatr* 2013;**172**:337—42.
8. Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease shock syndrome: a case—control study. *J Microbiol Immunol Infect* 2015;**48**:43—50.
9. Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of Kawasaki disease shock syndrome in Taiwan. *Pediatr Infect Dis J* 2013;**32**:1384—6.
10. Chang LY, Chang IS, Lu CY, Chiang BL, Lee CY, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 1996—2002. *Pediatrics* 2004;**114**:e678—82.
11. Huang WC, Huang LM, Chang IS, Chang LY, Chiang BL, Chen PJ, et al. Epidemiologic features of Kawasaki disease in Taiwan, 2003—2006. *Pediatrics* 2009;**123**:e401—5.
12. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014;**113**:148—54.
13. Beken B, Unal S, Cetin M, Gümrük F. The relationship between hematological findings and coronary artery aneurysm in Kawasaki disease. *Turk J Haematol* 2014;**31**:199—200.
14. Gatterre P, Oualha M, Dupic L, Iserin F, Bodemer C, Lesage F, et al. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med* 2012;**38**:872—8.
15. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;**118**:4041—52.
16. Kang HR, Kwon YH, Yoo ES, Ryu KH, Kim JY, Kim HS, et al. Clinical characteristics of hemophagocytic lymphohistiocytosis following Kawasaki disease: differentiation from recurrent Kawasaki disease. *Blood Res* 2013;**48**:254—7.
17. Yim D, Ramsay J, Kothari D, Burgner D. Coronary artery dilatation in toxic shock-like syndrome: the Kawasaki disease shock syndrome. *Pediatr Cardiol* 2010;**31**:1232—5.
18. Lin YJ, Cheng MC, Lo MH, Chien SJ. Early differentiation of Kawasaki disease shock syndrome and toxic shock syndrome in a pediatric intensive care unit. *Pediatr Infect Dis J* 2015;**34**:1163—7.