

Clinical Aspects for Recognitions of Kawasaki Disease Shock Syndrome in The COVID-19 Pandemic Era: A Case Control Study

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Abstract

Background As the COVID-19 pandemic continues, there have been reports of sudden increase of multi-system inflammatory syndrome in children (MIS-C) that shares clinical features with Kawasaki disease (KD). Recognition of sudden increase of severe Kawasaki-like disease is alarming the differential diagnosis of KD, Kawasaki disease shock syndrome (KDSS), septic shock, and toxic shock syndrome (TSS). To help clinicians distinguish KD, KDSS, septic shock, and TSS earlier, we suggest differential diagnosis and treatment guideline.

Methods Medical records of immunocompetent patients who were admitted to the pediatric department with a diagnosis of KDSS, septic shock or TSS (SS group) were retrospectively reviewed. In addition, KD patients were selected by seasonal matching to each case of KDSS patient by date of admission (\pm 2 weeks).

Results There were 13 patients with KDSS, 35 patients with SS group, and 93 patients with KD. In comparison between KDSS and septic shock group, KDSS group had significantly higher rate of higher incidence of coronary aneurysm, and higher left ventricle dysfunction rate. In comparison between KDSS and TSS, patients with KDSS had a significantly higher erythrocyte sedimentation rate (ESR) and significantly lower Creatinine. Receiver operation characteristic curve revealed that the optimal ESR cut off value for determining the KDSS was 56.0 (sensitivity 75.0%, specificity of 100.0%) and the optimal Creatinine cut off value for determining the TSS was 0.695 (sensitivity 76.9%, specificity 84.6%)

Conclusions Clinical symptoms, laboratory finding, echocardiography, and culture studies can be used to differentiate KD, KDSS, septic shock, TSS and MIS-C.

Background

Kawasaki disease (KD) is an acute systemic inflammatory vasculitis of early childhood, predominantly involving medium-sized arteries [1]. About 15–25% of untreated children will develop coronary artery abnormalities [2]. Early detection and prompt initiation of therapy with high dose intravenous immunoglobulin (IVIG) plus aspirin can reduce the incidence of serious coronary artery complications. Therefore, accurate and timely diagnosis of KD is critical. However, because of the absence of a specific diagnostic test and pathognomic clinical features, physicians must rely on the presence of specific clinical criteria and laboratory data that support the diagnosis of KD, while excluding other illnesses that could mimic the disease [3].

As the COVID-19 pandemic continues, there have been reports of multi-system inflammatory syndrome in children (MIS-C) that shares clinical features with KD [4]. Recognition of sudden increase of severe Kawasaki-like disease in the North America and European countries during the COVID-19 pandemic is alarming given unknown etiology of KD. Also, it is timely to address the differences in clinical manifestations between Kawasaki mimic diseases, some patients with KD may also present with hypotension or shock known as “Kawasaki disease shock syndrome” (KDSS). Differentiating between

KDSS and septic shock or toxic shock syndrome (TSS) in early stages of clinical diagnosis is challenging [1]. Although the clinical presentation of septic shock or TSS is comparable with that of KDSS, early diagnosis and initiation of treatment may be critical in patients with unstable conditions because clinical management is quite different.

Therefore, we retrospectively investigated patients admitted with diagnosis of KDSS, septic shock or TSS (SS group), and KD occurring in immunocompetent patients. Additionally, we tried to suggest KDSS differential diagnosis and treatment guideline.

Methods

Patient selection

A computerized search program was used to search for patients diagnosed with KD or KDSS or SS that occurred in immunocompetent patients from January 2004 to August 2019. These patients were classified into three groups: KDSS group, KD group, and SS group. 13 patients satisfied the KDSS criteria [5]. In KD group, control subjects were chosen for each case patient and matched to the case by date of admission (± 2 weeks) as the matching factor to control for the possibility of seasonal variation. Ninety-three patients met the inclusion criteria [6]. To search for patients with septic shock group, we searched "Septic shock" and "Toxic shock syndrome" from discharge records and immunocompromised patients were excluded. A total of 29 patients met the inclusion criteria for the septic shock or toxic shock syndrome.

This study used clinical data retrieved from Seoul National University Hospital Patients Research Environment system. This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB number: 1910-051-1068, approved date: Oct 14th, 2019).

Definitions

Diagnosis of KD was based on the diagnostic criteria provided by the American Heart Association (AHA) [7]. The diagnostic criteria were the presence of a fever lasting for at least five days and at least four of the following five clinical features typical of KD: bilateral bulbar conjunctival injection without exudate, erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, polymorphous rash and cervical lymphadenopathy (≥ 1.5 cm in diameter), usually unilateral. A diagnosis of incomplete or atypical KD was used for patients with a history of fever lasting for more than five days who had less than four of the five clinical features typical of KD but showing evidence of coronary artery lesion on echocardiography or compatible laboratory findings suggested by AHA [7]. KDSS was defined as a patient with KD complicated by hypotension without evidence of infection [5]. Hypotension was defined as a systolic blood pressure $< 5^{\text{th}}$ percentile for a patient's age. All patients with TSS were diagnosed by infection specialists using the diagnostic criteria provided by the Centers for Disease Control and Prevention (Supplement Table 1) [8]. Septic shock was defined as sepsis and cardiovascular organ dysfunction. Cardiovascular organ dysfunction means hypotension ($< 5^{\text{th}}$ percentile for age)

despite > 40 ml/kg fluid bolus in 1 hour or vasoactive requirement to maintain blood pressure despite > 40 ml/kg fluid bolus in 1 hour or two or more signs of abnormal perfusion (increased lactate, metabolic acidosis, decreased urine output (< 0.5 mL/kg/hr), capillary refill > 5 seconds) [9]. Organ damage was defined as damage occurring in major organs like brain, heart, lung, liver, and kidney due to hypoperfusion and uses a sequential organ failure assessment score as an index [10]. The coronary artery aneurysm was defined as Z score \geq 2.5. In the present study, patients with septic shock and TSS were assigned into the septic shock (SS) group.

Data collection

For all patients with KD, we accessed the following retrospectively collected data: demographic data (age, gender, associated symptoms and number of days of fever at presentation), laboratory values (white blood cell and differential counts, platelet count, erythrocyte sedimentation rate (ESR), and concentrations of hemoglobin, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransaminase (ALT), and γ -glutamyl transpeptidase (GGT), creatinine, blood urea nitrogen (BUN), albumin, electrolytes), laboratory evaluations of coagulation function, response to IVIG, oral prednisolone, methylprednisolone pulse therapy, and infliximab, and echocardiographic data. The laboratory data were compared to the worst values between 3 groups.

Statistical analysis

All data analyses were performed using SPSS statistics 25.0 (IBM, Armonk, NY, USA). Data are presented as median and ranges if not normally distributed. Not normally distributed data were compared between groups using the Mann-Whitney test, Fisher's exact test, or Chi-square test. One-way ANOVA was performed for continuous variables if normally distributed data. Kruskal-Wallis test was used to compare the laboratory data among more than two groups. Area under the ROC (receiver operating characteristic) curve was used as an accuracy index for the diagnosis of KDSS. As appropriate, $p < 0.05$ was considered significant.

Results

From January 2004 to August 2019, 13 patients were diagnosed as a KDSS. Over the same time, 13 patients were admitted with a diagnosis of TSS and 16 patients were admitted with a diagnosis of septic shock. In addition, 93 patients were treated by a KD.

Demographics and clinical characteristics of each group are shown in Table 1. Symptoms, diagnosis, and treatments of each group are shown in Table 2. All patients in the KDSS and KD group, and 17 of 29 patients in the SS group received an echocardiographic assessment. Laboratory values and ejection fraction for KDSS group and control groups are shown in Figure 1 and supplement table 2.

KDSS vs. KD vs SS group

Patients with KDSS had a significantly older age ($p = 0.00$), longer fever duration ($p = 0.008$), longer hospital day ($p = 0.00$), longer intensive care unit (ICU), admission days ($p = 0.00$), and higher rate of using inotropic drugs ($p = 0.00$) than patients with KD. (Figure 1, Table 1)

KD group had significantly higher rate of initial diagnosis of KD than those in the KDSS group and KDSS group initially showed only 1-2 of typical Kawasaki symptoms. However, finally 3 or more symptoms were seen in all patients. Patients with KDSS had significantly higher rate of conjunctival injection ($p = 0.00$), oropharyngeal changes ($p = 0.00$), cervical lymphadenopathy ($p = 0.00$), and extremity changes ($p = 0.001$) than patients with SS group. (Table 2) KDSS group had significantly higher gastrointestinal symptoms ($p = 0.00$), respiratory symptoms ($p = 0.00$), neurologic symptoms ($p = 0.013$), pantalgia ($p = 0.00$), pleural effusion ($p = 0.00$), and organ damage ($p = 0.00$) than those in the KD group. In addition, patients with KDSS had a significantly higher rate of respiratory symptoms ($p = 0.019$) and pleural effusion ($p = 0.029$) than patients with SS group. (Table 2)

Compared to those in the KD group, patients in the KDSS group had lower hemoglobin level ($p = 0.00$), lower platelet counts ($p = 0.00$), higher CRP level ($p = 0.00$), higher total bilirubin level ($p = 0.013$), higher creatinine level ($p = 0.002$), higher BUN level ($p = 0.00$), lower albumin level ($p = 0.00$), and lower sodium level ($p = 0.00$). Compared with patients with KDSS, patients with septic shock group had higher levels of creatinine ($p = 0.00$). However, there were no significant differences in hemoglobin, platelet count, CRP level, liver function, BUN, albumin or sodium level between KDSS and SS groups. Compared to patients with KD, patients with septic shock group had lower ESR ($p = 0.001$). Patients in the KDSS group had significantly higher IVIG resistance rate than those in the KD group. (Figure 1, Table 2, Supplement table 3)

Compared with patients with KD, left ventricle dysfunction represented by reduced ejection fraction ($< 55\%$) was more common in the KDSS group ($p = 0.00$). In addition, there was significantly ($p = 0.038$) more coronary artery aneurysm in the KDSS group than in the KD group. In the KDSS group, during the acute phase, five patients showed transient coronary artery aneurysm and three patients had persistent coronary artery aneurysm. In the KD group, during the acute phase of Kawasaki disease, 19 patients showed transient coronary artery aneurysm and four patients had persistent coronary artery aneurysm at the last echocardiography. There was no coronary artery aneurysm case in SS group. (Figure 1, Supplement Table 2)

KDSS vs TSS

There were no significant differences in age, sex-distribution, and laboratory findings between KDSS and TSS groups except for ESR and Creatinine. Patients with KDSS had a significantly higher ESR ($p = 0.019$) and significantly lower Creatinine ($p=0.007$) than patients with TSS. (Supplement Table 2) Receiver operation characteristic (ROC) curve revealed that the optimal ESR cut off value for determining the KDSS was 56.0 which had a sensitivity of 75.0% and a specificity of 100.0% (Figure 2, 3A, AUC, 0.894; 95% CI, 0.757-1.000, $P=0.003$) and the optimal Creatinine cut off value for determining the TSS was 0.695 which

had as sensitivity of 76.9% and a specificity of 84.6% (Figure 2, 3B, AUC, 0.802; 95% CI, 0.620-0.983, P=0.009).

Discussion

Because there is no pathognomonic clinical feature or diagnostic test for KD, patients with KDSS are frequently misdiagnosed. Its clinical presentation may be mistaken for septic shock or TSS, leading to delay in treatment [11]. In COVID-19 pandemic period, cases for MIS-C have been reported and shared clinical features with KD, KDSS, and TSS [4]. Case definitions for emerging inflammatory condition during COVID-19 pandemic from the World Health Organization, Royal College of Pediatrics and Child Health, and Centers for Disease Control and Prevention are similar in many ways to Kawasaki disease [12, 13, 14]. In COVID-19 pandemic era, to understand MIS-C by Lucio Verdoni et al, clinical features and laboratory findings were compared with each group [15]. (Supplement Table 2, 3, 4) We believe that this comparative analysis will help with the new diagnosis and treatment of MIS-C.

Considering the symptoms of KDSS that look different from KD and similar symptoms to other diseases such as TSS or MIS-C, the pathophysiological cause becomes curious. Despite 4 decades of investigation, the cause of KD remains unknown [7]. Recently updated three major pathophysiologic components of KD are a genetic predisposition, immunomodulation through both habitual exposures and environmental factors, and contact with the disease trigger or triggers [16]. In this background, exposure to the still unidentified trigger such as SARS-CoV-2 might result in the development of KD in a genetically susceptible child, with at least a partial contribution from immune-modulating factors. Multiple factors may act sequentially or simultaneously as predisposing, immune-modulating, or triggering agents, altering both individual risk as well as the incidence of KD in the population across countries or regions [16]. Recent reports of MIS-C suggest that MIS-C may have a different racial predilection, affecting primarily people of African American, Caribbean, and Hispanic ancestry [4].

The pathophysiology of KDSS is unknown, but it hypothesized that the “overexpression” of proinflammatory cytokines, in combination with an intense and systemic inflammation, leads to multiple organ damage and failure in KDSS. These clinical and laboratory findings suggest greater underlying inflammation with a more intense systemic vasculitis, capillary leak, and more profound myocardial involvement [1, 5, 11, 17].

In differentiation between KDSS, TSS, Septic shock, and MIS-C, septic shock and MIS-C can be diagnosed by blood culture and SARS-CoV-2 PCR or antibody test. Therefore, we agonized the differential diagnosis between KDSS and TSS and performed analysis of subgroup. In comparison of clinical manifestations between KDSS and TSS, no patients with TSS showed conjunctival injection or cervical lymphadenopathy and these findings could be differential points. In laboratory tests, highest ESR and creatinine level showed significant difference and possibility as useful marker for differential diagnosis in two groups. (Fig. 2, 3) These results are different from previous study and novel finding [1]. Since the diagnostic criteria for TSS include elevated creatinine, it is not surprising that the TSS group has a

significantly higher creatinine level. Since ESR level is proportional to the intensity of inflammation, it is estimated that more severe inflammatory immune response occurs in KDSS.

According to our comparison among each groups, specific symptoms and laboratory findings of each group are summarized in Supplement Table and Figure. Based on our clinical experiences, KDSS and SS group had many common findings. However, the KDSS group had Kawasaki symptoms, coronary dilation, and left ventricle dysfunction. These finding can help us differentiate KDSS from SS group. Based on our results, we can suggest a differential diagnosis and treatment guideline for KDSS (Fig. 4) [7].

Study Limitations

This study has several limitations. Our study was retrospective in nature and our case number was too small to analyze independent risk factors. This was a case-control study. KD patients were selected by seasonal matching to each case patient base on the date of admission within two weeks before and after. In addition, some patients were diagnosed by clinical manifestations. Thus, there could be a possibility of patient-selection bias.

Conclusions

KDSS should be considered for patients with fever, Kawasaki symptoms, and hypotension. Diagnosis and treatment for patients with KDSS may be more complicated because atypical type, gastrointestinal, respiratory, and neurological symptoms, and treatment resistant type are common. Clinical symptoms, laboratory finding, echocardiography, and serology or culture studies can be used to differentiate KDSS, SS, TSS and MIS-C. This study also suggested a guideline for diagnosis and treatment of KDSS.

List Of Abbreviations

AHA : American Heart Association

AST : Aspartate aminotransferase

ALT : Alanine aminotransaminase

BUN : Blood urea nitrogen

CRP : C-reactive protein

ESR : Erythrocyte sedimentation rate

GGT : γ -glutamyl transpeptidase

IVIG : Intravenous immunoglobulin

ICU : Intensive care unit

KD : Kawasaki disease

KDSS : Kawasaki disease shock syndrome

MIS-C : Multi-system inflammatory syndrome in children

SS group : Septic shock or toxic shock syndrome

TSS : Toxic shock syndrome

Declarations

Ethics approval and consent to participate

The ethics committee of the Institutional Review Board of the Seoul National University Hospital approved this retrospective study (IRB number: 1910-051-1068, approved date: Oct 14th, 2019) and waived the requirement for patient informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WYP: He is first author of this manuscript. He designed this study, analyzed and interpreted data, and drafted the manuscript and finally approved for submission.

GBK, MKS, HWK, EJB, EHC and JDP: They all analyzed and interpreted data and revised the manuscript and finally approved for submission.

SYL: He is corresponding author of this manuscript. He designed this study and analyzed and interpreted data, and revised the manuscript and finally approved for submission.

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Tables

Table 1

Demographics and clinical characteristics of patients with Kawasaki disease shock syndrome and control groups (continuous variables were described as median and range)

	KDSS (n = 13)	KD (n = 93)	SS (n = 29)	P value
Age, (years)	5.1 (0.5–10.6)	2.3 (0.2–8.4)	7.6 (0.3–19.9)	0.00
Male (%)	46.2% (6/13)	57.0% (53/93)	65.5% (19/29)	0.483
Fever duration (days)	11 (8–23)	8 (3–29)	7(1-114)	0.04
Total hospital day (days)	18 (6–31)	6 (3–18)	13(7-225)	0.00
Follow up duration (months)	10 (1-105)	13 (0-175)	2.5(0-119)	0.141
ICU care (%)	53.8% (7/13)	0.0% (0/93)	62.1% (18/29)	0.00
ICU care duration (days)	4 (0–11)	0 (0/93)	3(0–20)	0.707
Inotropic drugs (%)	92.3% (12/13) [§]	1.1% (1/93)	86.2% (25/29)	0.00
Respiratory support				
- No support	30.8% (4/13)	100% (93/93)	48.3% (14/29)	0.00
- Oxygen delivery	53.8% (7/13)	0.0% (0/93)	13.8% (4/29)	0.00
- Mechanical ventilation	15.4% (2/13)	0.0% (0/93)	37.9% (11/29)	0.00
Mortality (%)	0.0% (0/13)	0.0% (0/93)	10.3%(3/29)	0.015
KDSS = Kawasaki disease shock syndrome, KD = Kawasaki disease, SS = Septic shock and toxic shock syndrome, ICU = Intensive care unit				

Table 2

Symptoms, diagnosis, and treatment of Kawasaki disease shock syndrome, Kawasaki disease, and Septic shock group

	KDSS(n = 13)	KD(n = 93)	SS (n = 29)	P value
Kawasaki features				
Conjunctival injection	92.3% (12/13)	91.4% (85/93)	10.3% (3/29)	0.00
Oropharyngeal changes	84.6% (11/13)	81.7% (76/93)	17.2% (5/29)	0.00
Polymorphous rash	76.9% (10/13)	84.9% (79/93)	69.0% 1(20/29)	0.152
Cervical lymphadenopathy	69.2% (9/13)	43.0% (40/93)	3.4%(1/29)	0.00
Extremity changes	92.3% (12/13)	67.7% (63/93)	37.9% (11/29)	0.001
Associated symptoms				
Gastrointestinal symptoms	84.6% (11/13)	24.7% (23/93)	82.8% (24/29)	0.00
Respiratory symptoms	76.9% (10/13)	10.8% (10/93)	41.4% (12/29)	0.00
Neurologic symptoms	15.4% (2/13)	2.2% (2/93)	48.3% (14/29)	0.00
Pantalgia	53.8% (7/13)	3.2% (3/93)	37.9% (11/29)	0.00
Pleural effusion	76.9% (10/13)	2.2% (2/93)	41.4% (12/29)	0.00
Organ damage	92.3% (12/13)	21.5%(20/93)	82.8% (24/29)	0.00
Diagnosis				
Initial diagnosis of KD	23.1% (3/13)	80.6% (75/93)	0%(0/29)	0.0
Complete KD	46.2% (6/13)	67.7% (63/93)	0%(0/29)	0.00
Incomplete KD	38.5% (5/13)	29.0% (27/93)	0%(0/29)	0.01
Treatment				
1st IVIG	84.6% (11/13)	98.9% (92/93)	51.7% (15/29)	0.00
2nd IVIG	76.9% (10/13)	20.4% (19/93)	17.2% (5/29)	0.00
Oral prednisolone	7.7% (1/13)	10.8% (10/93)	0.0%(0/29)	0.00
Methylprednisolone pulse therapy	38.5% (5/13)	10.8% (10/93)	0.0%(0/29)	0.00
Infliximab	15.4% (2/13)	0.0% (0/93)	0.0%(0/29)	0.00
IVIG = Intravenous immunoglobulin, KD = Kawasaki disease, KDSS = Kawasaki disease shock syndrome, SS = Septic shock and toxic shock syndrome				

Figures

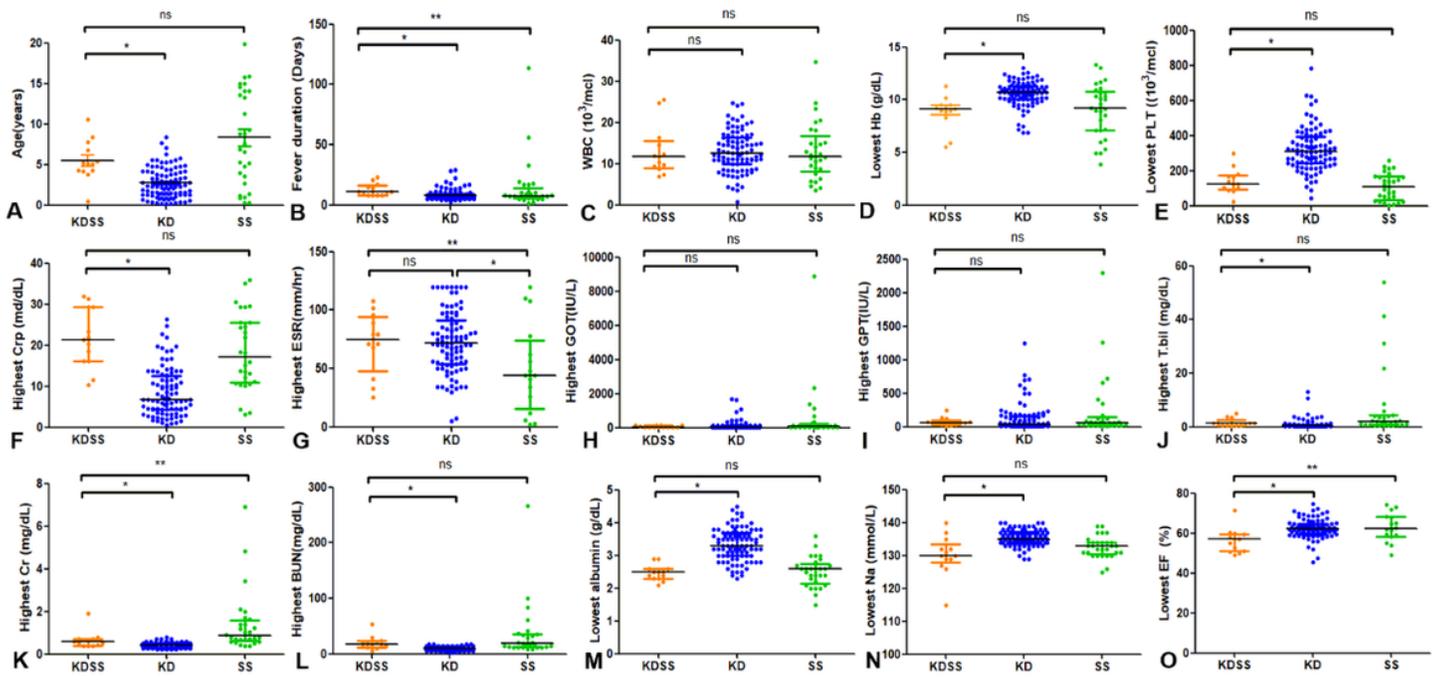


Figure 1

Comparison of Age, Fever duration, Laboratory Results and Ejection fraction in 3 Different Patient Groups. Statistics were calculated with GraphPad Prism software. Horizontal lines represent median values for each group and vertical lines represent interquartile range. *, **: statistically significant, ($p < 0.05$), as determined by the Kruskal-Wallis test ns : not significant

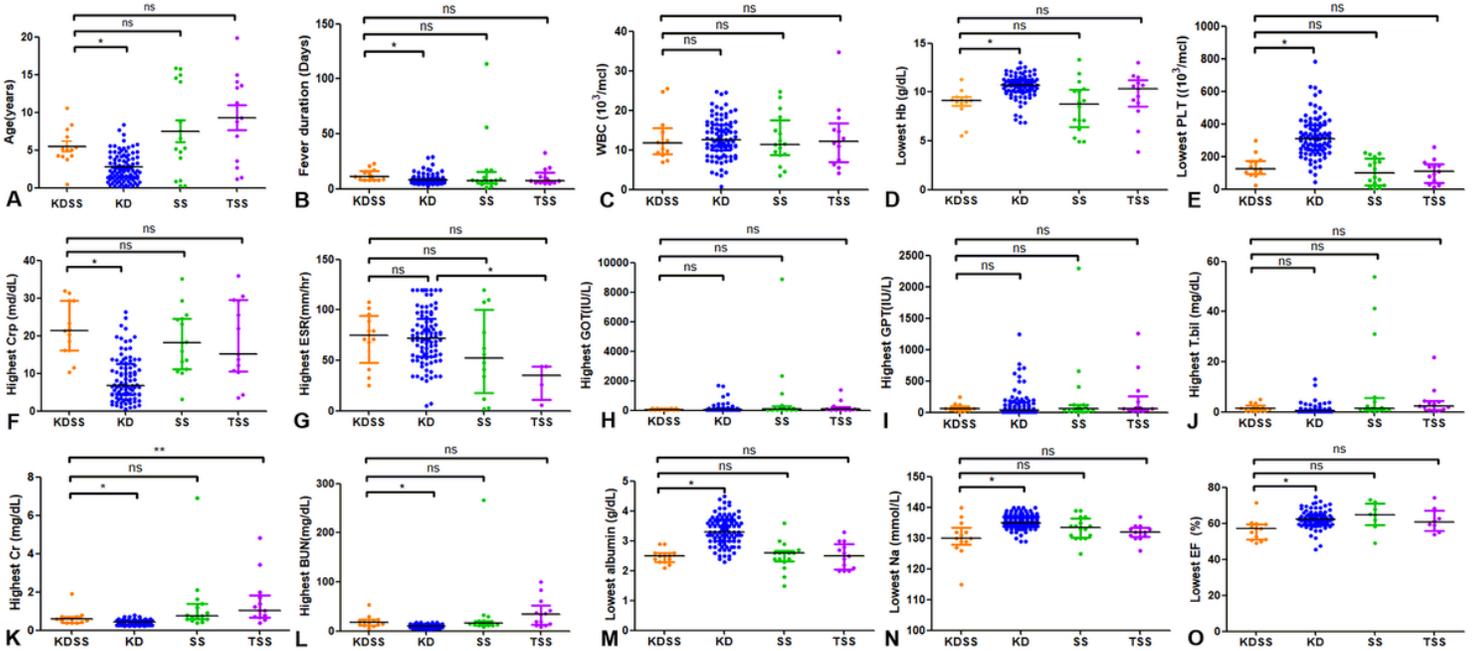


Figure 2

Comparison of Age, Fever duration, Laboratory Results and Ejection fraction in 4 Different Patient Groups. Statistics were calculated with GraphPad Prism software. Horizontal lines represent median values for each group and vertical lines represent interquartile range. *, ** : statistically significant, ($p < 0.05$), as determined by the Kruskal-Wallis test ns : not significant

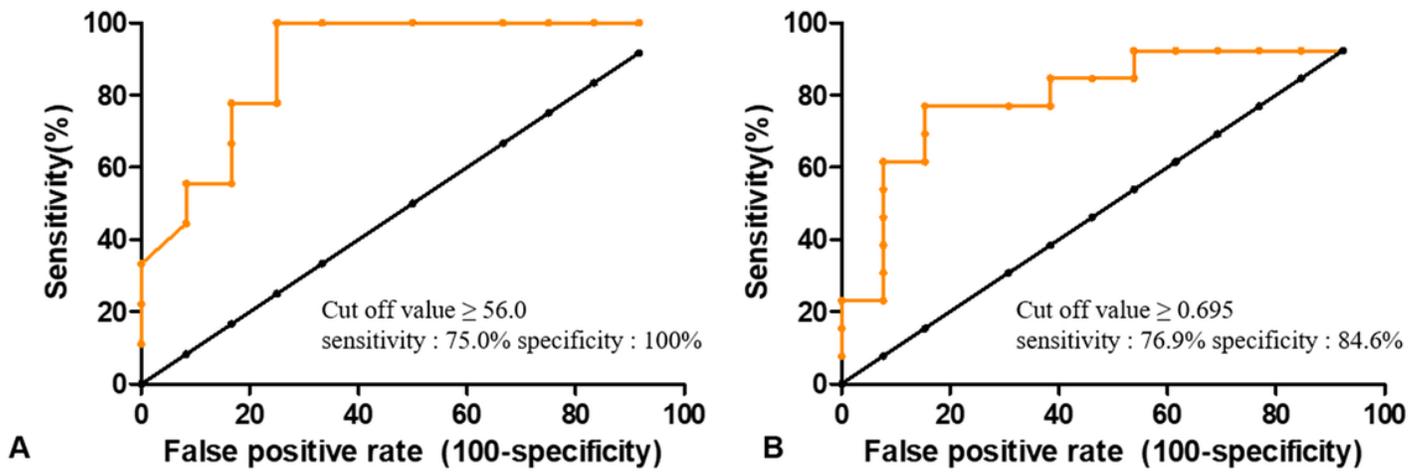


Figure 3

Receiver operation characteristic (ROC) curve and cutoff value for determining disease. (A) The optimal ESR cutoff for determining the KDSS ≥ 56.0 , sensitivity : 75.0% and specificity : 100.0%, AUC, 0.894; 95% CI, 0.757-1.000, $P=0.003$, (B) The optimal creatinine cutoff for determining the TSS ≥ 0.695 , sensitivity : 76.9% and specificity : 84.6%, AUC, 0.802; 95% CI, 0.620-0.983, $P=0.009$

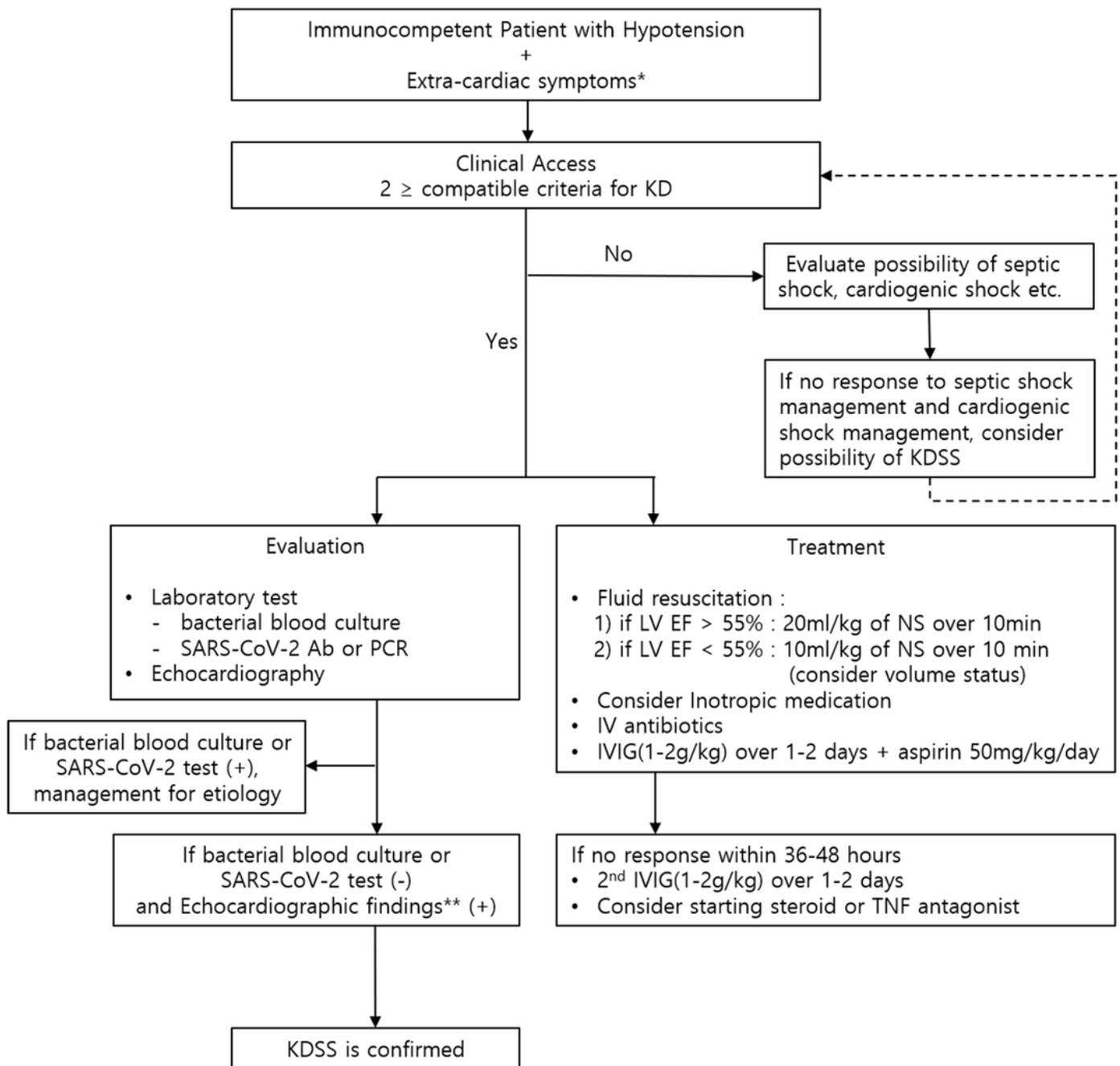


Figure 4

Diagnosis and treatment guideline suggested for Kawasaki disease shock syndrome. *Extra-cardiac symptoms were included gastrointestinal, respiratory, neurologic symptoms and pantalgia. **Coronary artery abnormality was defined from AHA scientific statement (6) IVIG = Intravenous immunoglobulin, NS = Normal saline, TNF = Tumor necrosis factor

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