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Research Article

Incidence and Outcomes of Kawasaki Shock Syndrome in United States: 2004-2014

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Abstract

Background: A subset of Kawasaki disease (KD) patients present with hypotension and shock, referred to as Kawasaki shock syndrome (KDSS). Little is known about KDSS in the US population. We sought to determine the incidence, predictors and outcomes of KDSS.

Methods: Using the Pediatric Health Information Systems dataset from 1/2004-3/2014, KDSS was defined as patients with KD who received IVIG and fulfilled ≥ 1 criteria for either ICD-9 diagnostic codes for shock; procedural/medication code for infusion of vasopressors, intensive hemodynamic monitoring, cardiopulmonary resuscitation, mechanical ventilation, or mechanical circulatory support. Clinical outcomes, additional drug use, mortality and hospital charges were compared using Chi square tests. Multivariate logistic regression was used to determine predictors of KDSS.

Results: Altogether 14,871 patients were admitted with acute KD, of which 1739 (11.7%) fulfilled criteria for KDSS. The predictors of KDSS include older age at presentation, non-Hispanic origin, abdominal signs/symptoms, concomitant bacterial/viral infection, sepsis and myocarditis. Patients with KDSS had significantly longer length of stay, higher rates of ICU admission, hospital charges, cardiac/renal complications and mortality ($P < 0.001$). Interestingly, only 27% of these patients with KD shock were treated in an ICU setting. KDSS patients had significantly higher use of additional anti-platelets, anti-coagulants, steroids and other immune modulators, antiarrhythmics, vasopressors, and anti-microbials ($P < 0.001$).

Conclusions: In a multi-institutional US cohort, shock accompanies 11.7% of acute Kawasaki admissions. KDSS patients are more likely to have serious adverse outcomes including mortality, coronary arterial changes, myocardial infarction, heart/renal failure, arrhythmia, need for transcatheter interventions, mechanical circulatory support and additional medical therapy.

Keywords: *Kawasaki Shock Syndrome; Kawasaki Disease; Intravenous Immunoglobulin; Intensive Care Unit*

Abbreviations

KDSS: Kawasaki Shock Syndrome; KD: Kawasaki Disease; ICD: International Classification of Diseases; PHIS: Pediatric Health Information System; IVIG: Intravenous Immunoglobulin; tPA: Tissue Plasminogen Activator; ICU: Intensive Care Unit

Introduction

Kawasaki disease (KD) is an acute vasculitis and a leading cause of acquired cardiovascular disease in children. In the United States, KD associated hospitalization rate for children ≤ 5 years has remained fairly constant over the last decade at ~17.1 per 100,000 children [1]. Although, the etiology of KD remains unknown, various infectious organisms/KD trigger(s) dispersed in the environment may cause predisposition in susceptible hosts [2,3]. Tsai., *et al.* [4] found that 66% of KD cases had positive contact with ill household members prior to their disease onset and 92% of families with KD had clusters of infectious illness.

Recent reports have noted the occurrence of shock and hypotension in the acute phase of KD and has been referred to as Kawasaki disease shock syndrome (KDSS) [5-9]. Although, the definition of KDSS has varied based on the study, it has been uniformly shown that patients with KDSS exhibit higher degree of inflammation [5,6,9-11], increased platelet consumption [6], higher degree of IVIG resistance [5,6,8,9,12], coronary artery dilation [5,7-9,12] and multi-organ dysfunction [10,13]. The factors leading to shock includes a spectrum of abnormalities including systemic inflammation, vasculitis, cytokine dysregulation, capillary leakage [13], valvulitis [14] and myocardial dysfunction [5,8].

Kanegaye., *et al.* [5] in their single center experience report that 7% (13 of 187 KD patients) had Kawasaki disease shock syndrome (KDSS) on the basis of systolic hypotension for age, a sustained decrease in systolic blood pressure from baseline of ≥ 20%, or clinical signs of poor perfusion [5]. A population based cross-sectional study performed in Taiwan by Lin and colleagues [7] utilizing an administrative database defined KDSS as patients with Kawasaki disease requiring intensive hemodynamic monitoring, administration of inotropic agents and resuscitation. They found an incidence of 1.45 KDSS for 100 patients with KD, which according to the study authors may be underestimated due to limitations in the diagnostic/procedural codes used in the study.

Previous small series of acute KD have shown that presence of moderate tricuspid regurgitation [14], initial diagnosis of toxic shock or septic shock [8] may be associated with admission into intensive care unit. Myocarditis can occur in 2 - 45% of acute KD patients [15,16]. Among all acute KD, the patients with shock more commonly exhibit mitral regurgitation (18 - 39%), pericardial effusion (27 - 46%), depressed ejection fraction < 54% (31 - 73%) and gastro-intestinal involvement (60 - 73%) [5,8,10-12]. However, the true incidence, predictors and outcomes of KDSS in United States remains unknown. Using a large administrative database, we sought to identify the incidence, predictors and outcomes of KDSS compared to non-shock KD in United States using a rigorous definition of KDSS.

Methods

All patients admitted with an International Classification of diseases, Ninth Revision (ICD-9), code for KD from January 2004 to March 2014 were collected from the pediatric health information system (PHIS) database. Pediatric Health Information System (PHIS), is an administrative database that contains inpatient, emergency department, ambulatory surgery and observation encounter-level data from over 48 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children's Hospital Association (Lenexa, KS). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (e.g. pharmaceuticals, imaging, and laboratory) into PHIS. Data are deidentified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study, data from 45 hospitals in US was included. This study was exempted from institutional review board.

Acute KD was defined as a patient with a diagnosis of Kawasaki disease and who received immunoglobulin (fulfilling either the drug or procedure code) during the current admission. KDSS included any patient with acute KD fulfilling ≥ 1 criteria for either shock; intensive hemodynamic monitoring including arterial catheter insertion or central venous catheter insertion; or administration of inotropic medication/resuscitation (Drug/Procedure/Diagnostic codes were used).

All subsequent admissions for KD were excluded from the analysis if they were identifiable. Among patients with KDSS those with ICD 9 diagnostic codes for iatrogenic hypotension from IVIG, anaphylactic reaction, other infusion/transfusion related reactions were excluded from the KDSS group and were analyzed under the non-shock category. The outcome measures included length of stay, ICU admission, cardiac complications (coronary changes, arrhythmia, heart failure, myocardial infarction), acute renal failure, diagnostic/interventional cardiac catheterization, mechanical circulatory support, any additional drug use beyond IVIG and aspirin, hospital charges and mortality.

The drugs were classified as follows: anti-platelet agents (dipyridamole, clopidogrel, ticlopidine, abciximab, eptifibatide), anti-coagulants (warfarin, heparin, enoxaparin, antithrombin, bivalirudin), steroids (dexamethasone, methylprednisolone, prednisone, prednisolone), fibrinolytic tissue plasminogen activator (tPA), immune modulators (Infliximab, anakinra, methotrexate, basiliximab, cyclosporine, cytarabine, daunorubicin, cyclophosphamide, dapsone, mycophenolate mofetil, sirolimus and tacrolimus), antiarrhythmics (Adenosine, Amiodarone, Atenolol, Propranolol, Flecainide, Procainamide, and Sotalol), vasopressors (Epinephrine, Norepinephrine, Dopamine, Dobutamine, and Milrinone), anti-microbials (anti-bacterial agents, anti-viral agents) and diuretics (Furosemide, Bumetanide, Chlorothiazide, Ethacrynic acid, Hydrochlorothiazide and Spironolactone).

Baseline characteristics and outcomes of KDSS and non-shock groups were compared using SPSS 23.0; Chi square, and Mann Whitney tests were used for categorical and continuous variables respectively. Multivariate logistic regression was used to determine predictors of KDSS.

Results

There were 14,871 admissions for acute KD, representing 1.8% of the total hospitalizations during the study period. We found that shock, as previously defined, was present in 11.7% (1,739) of the KD admissions. There was a decline in the incidence of KDSS from ~20% in 2004 to ~10% in recent years (Figure 1).

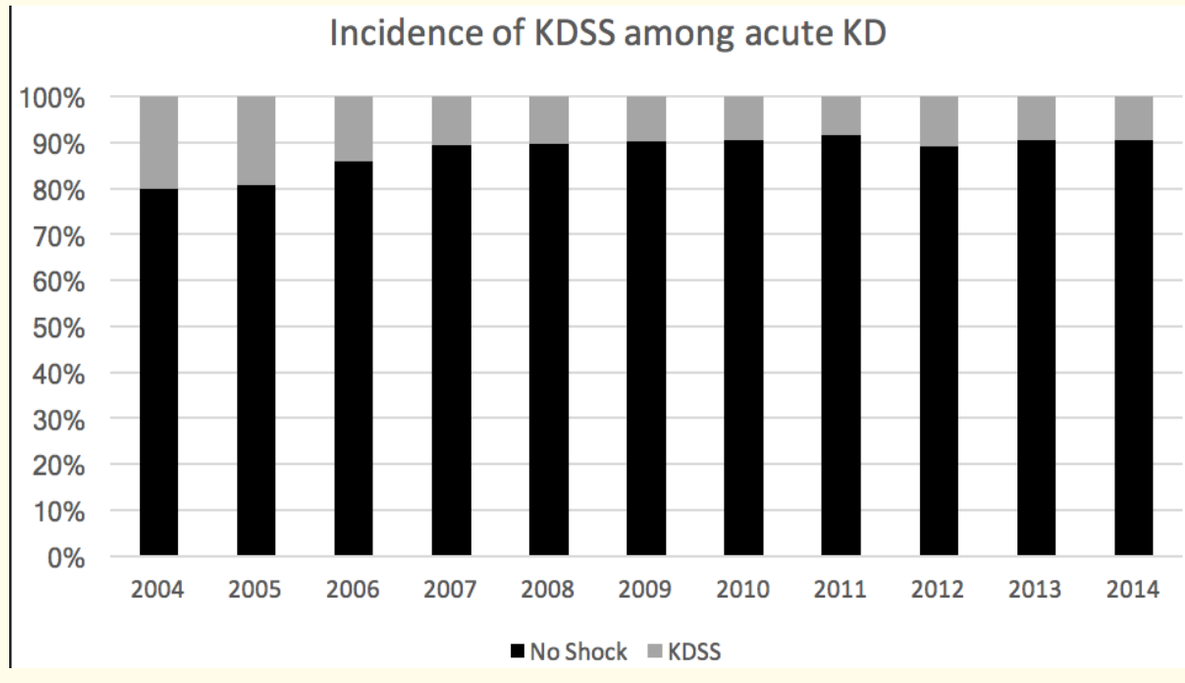

Figure 1: *Histogram showing the proportion of KD patients who present with shock versus non-shock.*

Among the 1,739 KDSS patients, 60% were male. Gender distribution was similar between the shock and non-shock group. KDSS patients presented at a median age of 3.1 (1.4 - 5.5) years whereas the median age was 2.7 (1.3 - 4.7) for the non-shock group; which does not appear clinically significant, although there was statistically significant difference ($P < 0.001$). KDSS patients were more likely to be non-Hispanic, have diagnostic codes for abdominal signs/symptoms including (abdominal pain, diarrhea, peritonitis, GI bleeding), bacte-

rial/viral infection, sepsis or myocarditis. In general, KD occurred more commonly during spring (March-May) and winter (November-February) and had a similar seasonal pattern across the shock and non-shock groups (Table 1).

		Kawasaki Shock syndrome		P Value
		No (n = 13132)	Yes (1739)	
Sex n (%)	Male Female	8017 (61.0) 5115 (39.0)	1037 (59.6) 702 (40.4)	0.255
Age years (IQ)	median	2.7 (1.3-4.7)	3.1 (1.4-5.5)	< 0.001*
Ethnicity n (%)	Hispanic Non-Hispanic Missing	2533 (19.3) 5753 (43.8) 4846 (36.9)	246 (14.1) 726 (41.7) 767 (44.2)	< 0.001
US Regions n (%)	Midwest Northeast South West	3430 (26.1) 1629 (12.4) 4597 (35.0) 3476 (26.5)	266 (15.3) 237 (13.6) 863 (49.6) 373 (21.4)	< 0.001
Discharge year n (%)	2004-08 2009-14	5625 (42.8) 7507 (57.2)	944 (54.3) 795 (45.7)	< 0.001
Discharge season n (%)	Spring Summer Fall Winter	3769 (28.7) 2661 (20.3) 2683 (20.4) 4019 (30.6)	507(29.2) 352 (20.2) 338 (19.4) 542 (31.2)	0.797
Overall abdominal findings n (%)	 Abdominal pain Vomiting Diarrhea Peritonitis GI bleeding	776 (5.9) 109 (0.8) 305 (2.3) 415 (3.2) 49 (0.4) 34 (0.3)	155 (8.9) 35 (2.0) 47 (2.7) 86 (4.9) 24 (1.4) 13 (0.7)	< 0.001 < 0.001 0.327 < 0.001 < 0.001 < 0.001
Overall associated infection n (%)	 Bacterial Viral	2078 (15.8) 617 (4.7) 1051 (8.0)	384 (22.1) 139 (8.0) 159 (9.1)	< 0.001 < 0.001 0.102
Sepsis n (%)		45 (0.3)	179 (10.3)	< 0.001
Myocarditis n (%)		69 (0.5)	109 (6.3)	< 0.001

Table 1: *Demographics and presenting features of KDSS versus non-shock patients.*

**: p-value using Mann Whitney test; Other p-values were performed using Chi-Square test in two or > 2 categorical variables.*

In a multivariate logistic regression model, factors including older age at presentation, diagnosis in the first 5 years of the study period (versus last 5 years), being non-Hispanic, presence of abdominal pain, diarrhea and peritonitis, gastrointestinal (GI) bleed, associated bacterial/viral infection, myocarditis and sepsis were independently associated with KDSS (Table 2).

	Odds Ratio (95% CI)	P value
Age years	1.05 (1.03, 1.08)	< 0.001
Discharge years 2004-08	1.77 (1.48, 2.12)	< 0.001
Ethnicity Non-Hispanic	1.54 (1.30, 1.84)	< 0.001
Abdominal findings		
Abdominal pain	2.67 (1.64, 4.33)	< 0.001
Diarrhea	1.41 (1.02, 1.95)	0.037
Peritonitis	2.32 (1.19, 4.49)	0.013
Infection (bacterial/viral)	1.21 (1.02, 1.44)	0.026
Sepsis	36.71 (24.79, 54.36)	< 0.001
Myocarditis	14.35 (9.57, 21.52)	< 0.001
US Regions		
Northeast	2.67 (2.09, 3.41)	< 0.001
South	2.23 (1.82, 2.73)	< 0.001
West	1.37 (1.08, 1.73)	0.009

Table 2: *Multivariate logistic regression showing all the variables that were independently associated with development of KDSS.*

All clinical outcomes including length of stay, hospital charges, ICU admission, cardiac complications (coronary arterial changes, myocardial infarction, heart failure, arrhythmia), acute renal failure, mortality, need for transcatheter interventions, mechanical circulatory support, infusion of blood products, dialysis and plasmapheresis were significantly more common in the KDSS patients (Table 3 and 4).

	Kawasaki Shock syndrome		P Value
	No (n = 13132)	Yes (1739)	
Length of stay days median (IQ 25 - 75%)	3 (2-4)	4 (2-7)	< 0.001
Hospital charges days median (IQ 25 - 75%)	$ 8760 (5835-12707)	$ 11227 (6333-23579)	< 0.001
ICU admission			
No n (%)	12672 (96.5)	1262 (72.6)	< 0.001
Yes	460 (3.5)	477 (27.4)	
Cardiac complications			
Coronary changes	1073 (8.2)	197 (11.3)	< 0.001
MI, Heart failure	146 (1.1)	98 (5.6)	< 0.001
Arrhythmias	196 (1.5)	69 (4)	< 0.001
Acute renal failure	21 (0.2)	59 (3.4)	< 0.001
Mortality	0	6	< 0.001

Table 3: *Primary outcomes of KDSS versus non-shock patients.*

	Kawasaki Shock syndrome		P Value
	No (n = 13132)	Yes (1739)	
Diagnostic Cath n (%)	30 (0.2)	26 (1.5)	< 0.001
Transcatheter interventions n (%)	8 (0.1)	6 (0.3)	< 0.001
Mechanical support n (%)	2	117 (6.7)	< 0.001
Infusion of blood products n (%)	158 (1.2)	192 (11.0)	< 0.001
Blood transfusion	149 (1.1)	182 (10.5)	< 0.001
Platelets, Coagulation factors	8 (0.1)	22 (1.3)	< 0.001
Albumin	101 (0.8)	269 (15.5)	< 0.001
Other serum products	11 (0.1)	31 (1.8)	< 0.001
Dialysis n (%)	2	11 (0.6)	< 0.001
Plasmapheresis n (%)	0	3 (0.2)	< 0.001

Table 4: *Need for additional interventions among the KDSS compared to non-shock patients.*

All patients received IVIG and 90% received aspirin. Of those who did not receive aspirin 6.7% had abdominal symptoms, and 19% had associated viral/bacterial infection. Use of all additional drugs including other anti-platelet agents, anti-coagulants, steroids, fibrinolytic tissue plasminogen activator (tPA), immune modulators, antiarrhythmics, vasopressors, anti-microbials and diuretics were significantly more common in the KDSS population (Supplementary Table 1).

	Kawasaki Shock syndrome		P Value
	No (n = 13132)	Yes (1739)	
Aspirin n (%)	11648 (88.7)	1558 (89.6)	0.267
Other antiplatelets	124 (0.9)	42 (2.4)	< 0.001
Anticoagulants	150 (1.1)	59 (3.4)	< 0.001
Steroids	795 (6.1)	357 (20.5)	< 0.001
Fibrinolytic tPA	31 (0.2)	80 (4.6)	< 0.001
Immune modulators	248 (1.9)	101 (5.8)	< 0.001
Antiarrhythmics	2601 (19.8)	449 (25.8)	< 0.001
Vasopressors	21 (0.2)	1383 (79.5)	< 0.001
Antimicrobials	4441 (33.8)	943 (54.2)	< 0.001
Diuretics	291 (2.2)	362 (20.8)	< 0.001

Supplementary Table 1: *Additional drug use beyond IVIG in KDSS versus non-shock patients.*

tPA: Tissue Plasminogen Activator

Discussion

KDSS is an under-recognized entity and previous authors have reported variable prevalence of KDSS among acutely hospitalized KD patients, ranging from 1.5 - 7% [5-8,13]. This may be due to variable/limited case definition of KDSS in previous reports and more inclusive definition here using administrative database. Previous studies limited to single centers, defined KDSS as those with acute KD complicated by systolic hypotension for age or clinical signs of poor perfusion, without evidence of infection and requiring intensive care.

Hypotension is hard to define as normative data for the lower limits of BP in small children is not well established [17,18] and shock can occur with normal, increased or decreased systolic blood pressure. Besides, BP measurements can be challenging in irritable critically ill children and even in the non-shock KD patients. We therefore thought there was a need to devise a more inclusive shock definition for the purposes of this study. Hence, in addition to hypotension our shock definition included ICD-9 diagnostic code for cardiogenic shock, septic shock, acidosis, toxic shock syndrome, oliguria, anuria, volume depletion and hypovolemia, procedural/medication code for infusion of vasopressors, intensive hemodynamic monitoring, cardiopulmonary resuscitation, mechanical ventilation, or mechanical circulatory support.

We noted a significantly higher incidence of KDSS of 11.7% compared to the few limited US studies and the larger database Taiwanese study. Our data suggests that over the last decade there is a dramatic decline in the incidence of KDSS from ~20% in earlier years to ~10% more recently (Figure 1). In contradiction to the Taiwanese study, we used additional ICD-9 diagnostic code for septic shock, acidosis, toxic shock syndrome, oliguria, anuria, volume depletion and hypovolemia. It is also possible, that the true incidence of KDSS may be different in the USA versus Taiwan. Additionally, the findings could be related to the pattern of charting with ICD 9 codes which may be entered by non-medical administrative staff or could be accounted for by the decrease in frequency of invasive procedure code related to intensive care utilized in the care of these patients. Over this period of time electronic medical records became much more popular where physicians are choosing the billing codes thus more recent data may be more accurate.

In contrast to the study by Kanegaye., *et al.* [5] where Hispanic ethnicity comprised 54% of the KDSS population, we found a significant association of KDSS with non-Hispanic ethnicity. Non-Hispanic blacks had the highest odds (OR 1.83) of developing KDSS, followed by non-Hispanic Asians (1.62), and non-Hispanic white (1.22). Genetic differences may confer varying predisposition to development of KDSS [2] but with incomplete reporting of race/ethnicity (data was available in only 62% of the patients) it is hard to clarify this question using this data. Older age at presentation (OR 1.05), abdominal signs/symptoms including abdominal pain, diarrhea, peritonitis, GI bleeding, associated bacterial infection, sepsis and myocarditis were independent predictors of development of KDSS. Supported by findings from previous studies showing higher degree of inflammation evidenced by blood markers (like bands, higher C reactive protein, and lower hemoglobin) [5,7], we believe that the inflammatory cascade is responsible for systemic capillary leak, gastrointestinal mucosal derangement leading to abdominal signs/symptoms and bacterial translocation into blood stream leading to sepsis and shock.

KDSS represents a sicker group of patients requiring more frequent ICU admissions and longer lengths of hospital stay and hospital charges. Interestingly 72% of the KDSS patients were treated in a non-ICU setting of which 76.4% received inotropic support. We speculate that low dose inotropes such as Epinephrine/Dopamine/Dobutamine could have been administered in the emergency room setting, and following improvement in clinical condition, such patients may have received care in step down units (these may not qualify as ICU for diagnostic code purpose or there may be errors in coding). Another plausible theory is that inotropes could have been ordered, and billed but never administered to the patient. Cardiac complications including (coronary changes, myocardial infarction, heart failure and arrhythmia), acute renal failure and mortality was significantly associated with KDSS. Hence, it is logical that this select group of patients were more likely to undergo transcatheter interventions, mechanical circulatory support, infusion of blood products, dialysis and plasmapheresis.

Although, IVIG was used for all patients by case definition, aspirin was used in only 90% of the cases. In this selected group of patients that did not receive aspirin, providers may have withheld aspirin for suspicion of bacterial/viral infection (19%), presence of abdominal signs/symptoms (6.7%) or due to concomitant steroid use (7%). Coagulopathy and/or liver derangement may be other reasons for withholding aspirin but those could not be analyzed from the available data. All other drugs including second line anti-platelets, anticoagulants, steroids, fibrinolytics (tPA), immune modulators, antiarrhythmics, vasopressors, anti-microbials and diuretics were more commonly used in the KDSS group.

Limitations of this study include its definition of KDSS, its retrospective nature, using an administrative database where the participating hospitals may have changed during the study period. At this time KDSS is poorly defined and studies have used different inclusion criteria. This must be better defined. The information was dependent on accuracy of charting, billing and ICD 9 codes. There was inadequate information on clinical symptoms which may not be coded, 38% of patients were missing data on race/ethnicity and there are no recorded vitals and laboratory values available in this type of administrative data. Hence, we were not able to differentiate between complete versus incomplete presentation of KD. Also, echocardiographic details are not included in this database. Hence, it was not possible to accurately compare coronary findings, systolic versus diastolic dysfunction, the presence of valvulitis or pericarditis. Additionally, the outcomes described only relate to the hospitalization thought to be for the acute phase of KDSS as described above, and does not examine later clinical course. The PHIS database does not allow one to analyze the temporal sequence of events and treatments during a hospitalization. There may be some patients who acquired a diagnostic code for KD early in the hospitalization when a definitive diagnosis had not been made and the code was not removed.

Further refinement of the KDSS definition and standardization of treatment algorithm for KD patients who present in shock will help to improve knowledge about the disease and potentially clinical outcomes.

Conclusion

In the US, acute Kawasaki disease is accompanied by shock (as defined herein) in 11.7% of cases and there has been a marked decline from ~20% to ~10% over the last decade. The predictors of KDSS include older age at presentation (> 3 years), non-Hispanic origin, concomitant bacterial/viral infection, and abdominal signs/symptoms. These patients are likely to have serious complications including coronary artery changes, myocardial infarction/heart failure requiring mechanical circulatory support, transcatheter interventions, infusion of blood products, longer hospitalization and mortality. Additional medical treatment beyond IVIG and aspirin occurs in these patients and in conjunction with above factors are associated with increased healthcare charges.

Potential Conflict of Interest

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

Financial Disclosure

The authors have indicated they have no financial relationships relevant to this article to disclose.

Authors' Contribution

All the listed authors have made significant contribution in the preparation and review of the manuscript.

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