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Research Article

Characteristics and Outcomes of Children with Systemic Inflammatory Response Syndrome due to Sepsis and non-Sepsis in a Tertiary Care Center in Thailand

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Abstract

Aim: Our aim was to describe the clinical characteristics and outcomes of systemic inflammatory response syndrome (SIRS) in children due to sepsis and non-sepsis, and evaluate factors associated with hospital mortality among children with SIRS and sepsis.

Methods: A prospective observational study was conducted at a tertiary care center in Thailand. Eligible patients were <18 years old with at least two SIRS criteria per standard guidelines and had hemoculture within 48 hours of SIRS presentation. Patients' characteristics, laboratory results, and clinical outcomes were compared between children with sepsis and non-sepsis SIRS. Multivariable logistic regression analyses were performed to assess risk factors associated with mortality in patients with SIRS and sepsis.

Results: Of 229 children included, 177 (77.3%) had sepsis. Post-operation was the most common cause of non-sepsis SIRS. Nosocomial infections were responsible for 56.5% of sepsis cases. The mortality rate due to sepsis was 8.5%, and catheter-related bloodstream infection was the only factor associated with in-hospital mortality among children with sepsis (adjusted odds ratio 3.6 (95% confidence interval 1.1-12.2). Patients with SIRS from sepsis had significantly higher intubation rate compared to those from non-sepsis causes, 21.5% vs 0% (p<0.001), while ICU admissions (27.7% vs 17.3%, p=0.130), length of stay (median 15 vs 8 days, p=0.234), and mortality rate (8.5% vs 3.8%, p=0.373) were higher but not statistically significant.

Conclusion: Sepsis is the primary cause of SIRS in children, and nosocomial infection was responsible for half of sepsis cases in our setting. Children presenting with SIRS should trigger empirical sepsis management.

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Keywords: systemic inflammatory response syndrome; sepsis; mortality rate; bacteremia

Abbreviations

CRBSI	catheter-related bloodstream infection
IQR	interquartile range
OR	odds ratio
PCT	procalcitonin
RSV	respiratory syncytial virus
SIRS	systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment

Introduction

Systemic inflammatory response syndrome (SIRS) is a condition caused by the human body's response to noxious stimuli. When the stimuli enter the body, multiple cytokines are secreted in response, causing inflammation. Although the body has the capacity to elicit an anti-inflammatory reaction to maintain an equilibrium, if the inflammation progresses such that this equilibrium is lost, multi-organ failure and other serious consequences can occur. While the most common cause of SIRS is infection it may also be precipitated by other etiologies, such as surgery, major trauma, burn, medications, organ ischemia, and cancer.

Previous evidence has shown that approximately 47% of adult patients developed symptoms compatible with SIRS at least once during their hospital stay.[1] However, the incidence of SIRS in pediatric patients admitted to the intensive care units (ICU) was as high as 68%, with two-thirds due to infection.[2]

Sepsis is defined as SIRS in the presence of infection.[3] It is one of the most critical emergency conditions in pediatric and adult patients, resulting in high morbidity and mortality rates. Early diagnosis and aggressive treatment management are mandatory to prevent severe complications and mortality. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) recommends using the Sequential Organ Failure Assessment (SOFA) score of at least 2 with the presence of infection to diagnose sepsis in adults,[3] whereas in pediatrics, the criteria for the diagnosis of sepsis consists of the presence of infection and at least 2 out of the 4 SIRS criteria.[4]

With earlier diagnosis and timely-delivered antibiotic and supportive management based on early goal-directed therapy,[5,6] the mortality rate due to sepsis has decreased from 37.7% to 10.4%.[7] It is critical to detect SIRS early and provide empirical treatment for sepsis.

Although SIRS is still the main criteria to diagnose sepsis in children, it has always been known for its poor specificity for sepsis. Also, little is known about the difference in characteristics and outcomes of children with SIRS caused by sepsis or other causes. We conducted an observational study to evaluate the characteristics and outcomes of pediatric patients with SIRS due to sepsis and patients with SIRS from other causes. We also evaluated factors associated with hospital mortality in those with SIRS and sepsis.

Methods

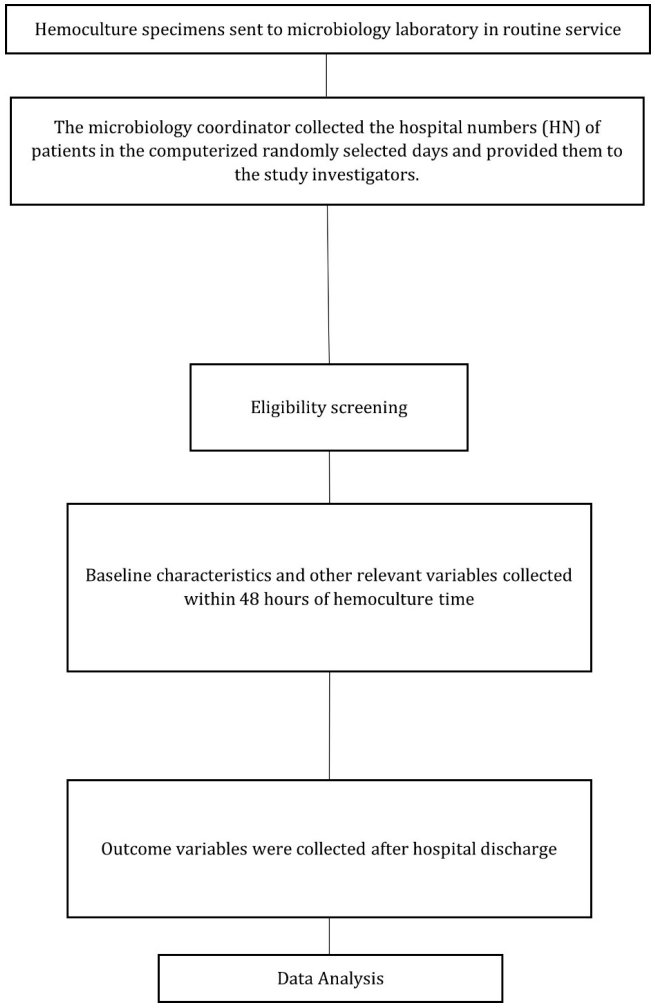
This prospective observational study was conducted between January 1 and December 31, 2019 at Siriraj Hospital, a large tertiary university hospital in Bangkok, Thailand. The Department of Pediatrics has a total of 300 in-patient beds, including 12 ICU beds. The department provided care for 94,223 out-patient and 8,154 in-patient cases in 2019. The institutional review board approved this study [Si597/2019]. A waiver of informed consent was approved for this study as it was the observational study, the risk to subjects was deemed minimal and it that did not adversely affect the management or the rights and welfare of the subjects.

Eligible patients were those younger than 18 years of age who met at least two SIRS criteria using the standard guidelines[4] and had hemoculture obtained within 48 hours of SIRS presentation.

During the study period, the investigators randomly selected two out of seven days each week for participant recruitment based on a computer-generated sequence. On the randomly-selected recruitment day, the study investigators identified potential subjects from a list of patients who had hemoculture ordered in routine care provided by the microbiology laboratory coordinator. The investigators then reviewed patients' current medical records for the presence of SIRS criteria. If the inclusion criteria were met, patients were recruited into the study. Baseline characteristics and demographics were recorded, such as age, sex, body weight,

height, underlying diseases, and current medications. In cases of sepsis, the primary sources of infection and hemoculture results were documented. During the participants' hospital stay, clinical management was at the discretion of the attending physicians. The data of relevant laboratory investigations and other variables associated with the diagnosis and treatment including vasopressor prescription, endotracheal intubation, pediatric ICU admission, mortality, and hospital length of stay were retrospectively collected after the participants were discharged. All the study data were imputed and stored in a secured electronic database. The flow of the study processes and data collection are summarized in Figure 1.

Figure 1.Description of the Study Process and Data Collection



Statistical analyses

Baseline characteristics are described using descriptive statistics. Continuous variables are reported with median and interquartile range (IQR) or minimum and maximum values and compared using the Mann-Whitney U test. Categorical variables are reported as frequency and percentage. The Chi-squared, Fisher's exact, or Kruskal-Wallis rank test was used to compare categorical variables as appropriate. Univariable and multivariable logistic regression analyses were performed to determine factors associated with mortality in patients with SIRS and sepsis. Results are presented as odds ratio (OR) for univariable analyses and adjusted OR for multivariable analyses. All statistical analyses were performed using STATA Version 11.2 (Stata Corp LP, TX, USA).

Results

Characteristics of SIRS

Between January to December 2019, a total of 446 children who had hemoculture obtained were screened, 229 (51.3%) had SIRS. Among children with SIRS, 177 (77.3%) had sepsis, of which 18 (10.1%) had septic shock. Non-sepsis causes of SIRS included post-operation or procedure (n=20 (38.5%)), chemotherapy or vaccine (n=9 (17.3%)), newborn-related conditions (n=8 (15.4%)), and others (n=15 (28.8%)), Figure 2A.

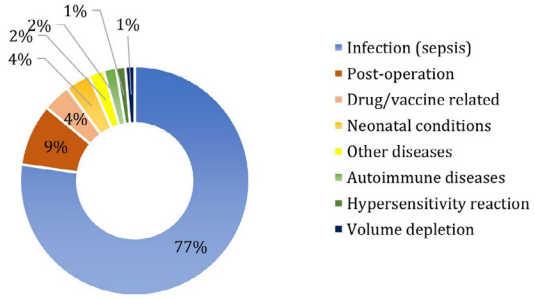


Figure 2A: Etiologies of systemic inflammatory response syndrome

Of patients with SIRS, 120 (52.4%) were male, and 167 (72.9%) had underlying diseases, Table1. The most common underlying diseases were congenital heart diseases (27.5%), hematologic diseases (21%), cancer (13.8%), gastrointestinal and biliary tract diseases (12.6%), and neurological conditions (8.4%).

Eighty-three (36.2%) patients were immunocompromised.

Characteristics and outcomes of patients with sepsis

Among the 177 patients with sepsis-induced SIRS, 67 (37.9%) were immunocompromised, and 100 (56.5%) suffered from nosocomial infection. The most common primary source of infection was the respiratory tract (39%), followed by primary bacteremia (16.4%), Figure 2B.

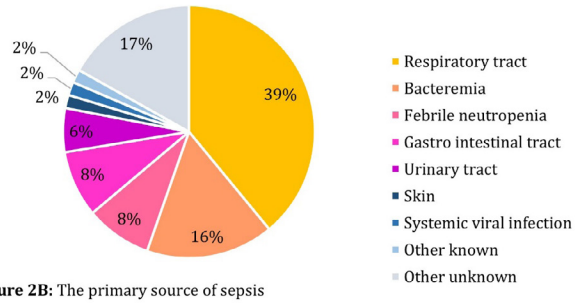


Figure 2B: The primary source of sepsis

The etiologic pathogens were identified in 92 (52%) patients with sepsis: bacteria in 59 (33.3%), followed by viruses in 31 (17.5%) and fungi in 4 (2.3%) patients. The bacterial pathogens were discovered from blood culture in 38 (21.5%) children, 21 (55.3%) of which were due to catheter-related bloodstream infection (CRBSI). *A. baumannii, P. aeruginosa,* and *K. pneumoniae* were the three most common bacterial pathogens isolated. The empirical antibiotic treatment was effective in 27 (71%) patients. Among viral pathogens, influenza and respiratory syncytial virus (RSV) were the most prevalent organisms. Compared to older children, infants less than 2 months were more likely to have sepsis with shock (28.6% vs 7.7%, p = 0.003) or require ICU admission (71.4% vs 21.8%, p <0.001), but less likely to have underlying diseases (47.6% vs 78.2%, p = 0.003) (Table 2).

Table 1: Participants baseline characteristics and outcomes by the sepsis or non-sepsis SIRS.

Characteristics	SIRS (N=229)	Non-sepsis (N=52)	sepsis (N=177)	P-value Sepsis vs non-sepsis
Underlying diseases				
yes	167 (72.9)	35 (67.3)	132 (74.6)	0.300
no	62 (27.1)	17 (32.7)	45 (25.4)	
Immunity status				
Deficit	83 (36.2)	16 (30.8)	67 (37.9)	0.350
Normal	146 (63.8)	36 (69.2)	110 (62.1)	
Sex				
Male	120 (52.4)	25 (48.1)	95 (53.7)	0.478
Female	109 (47.6)	27 (51.9)	82 (46.3)	
Age (months)	24 (8-84)	30 (8-72)	24 (7-84)	0.958
Procalcitonin (n)	45	10	35	
Median (IQR), ng/mL	2 (0.7-9.2)	3.5 (1.6-6.9)	1.6 (0.6-9.5)	0.557
Min, max, ng/mL	0.08, 100	0.09, 42.7	0.08, 100	
Hospital length of stay, days	12 (6-43)	8 (5-36)	15 (7-44)	0.234
Endotracheal intubation				

Yes	38 (16.6)	-	38 (21.5)	<0.001
No	191 (83.4)	52 (100.0)	139 (78.5)	
Vasopressive agents				
Yes	35 (15.3)	5 (14.3)	30 (85.7)	0.196
No	194 (84.7)	47 (24.2)	147 (75.8)	
Intensive care unit admission				
Yes	58 (25.3)	9 (17.3)	49 (27.7)	0.130
No	171 (74.7)	43 (82.7)	128 (72.3)	
Mortality				
Yes	17 (7.4)	2 (3.8)	15 (8.5)	0.373
No	212 (92.6)	50 (96.2)	162 (91.5)	

Data are presented as n (%) or median (interquartile range). SIRS; systemic inflammatory response syndrome

Table 2: Baseline characteristics and outcomes of participants with SIRS caused by sepsis by age.

Characteristics	All (n=177)	<2 months (n=21)	>2 months to <1 year (n=36)	>1 to <5 years (n=56)	>5 years (n=64)	p-value
Underlying diseases **Yes** **No**	132 (74.6) 45 (25.4)	10 (47.6) 11 (52.4)	24 (66.7) 12 (33.3)	42 (75) 14 (25)	56 (87.5) 8 (12.5)	0.002
Immunity status **Deficit** **Normal**	67 (37.9) 110 (62.1)	1 (4.8) 20 (95.2)	6 (16.7) 30 (83.3)	25 (44.6) 31 (55.4)	35 (54.7) 29 (45.3)	<0.001
Sex **Male** **Female**	95 (53.6) 82 (46.3)	12 (57.1) 9 (42.9)	16 (44.4) 20 (55.6)	34 (60.7) 22 (39.3)	33 (51.6) 31 (48.4)	0.463
Septic shock	18 (10.2)	6 (28.6)	3 (8.3)	3 (5.4)	6 (9.4)	0.046
Type of infection **Community-acquired** **Nosocomial**	77 (43.5) 100 (56.5)	5 (23.8) 16 (76.2)	13 (36.1) 23 (63.9)	30 (53.6) 26 (46.4)	29 (45.3) 35 (54.7)	0.089

Primary source of sepsis						
Respiratory tract	69 (39)	7 (33.3)	18 (50)	25 (44.6)	19 (29.7)	
Bacteremia	29 (16)	3 (14.3)	8 (22.2)	9 (16.1)	9 (14.1)	
Febrile neutropenia	15 (8.5%)	0	0	5 (8.9)	10 (15.6)	
Gastrointestinal tract	15 (8.5%)	2 (9.5)	4 (11.1)	3 (5.4)	6 (9.4)	
Urinary tract	10 (5.6)	1 (4.8)	1 (2.8)	4 (7.1)	4 (6.3)	
Skin infection	3 (1.7)	1 (4.8)	0	0	2 (3.1)	
Systemic viral infection	3 (1.7)	0	0	2 (3.6)	1 (1.6)	
Others	3 (1.7)	0	1 (2.8)	0	2 (3.1)	
Unknown	30 (17)	7 (33.3)	4 (11.1)	8 (14.3)	11 (17.2)	
Hospital length of stay, days	15 (7-44)	24 (17.5-62)	16 (9-95.5)	10.5 (4-34)	15 (6.5-40.5)	0.055
ICU admission	49 (27.7)	15 (71.4)	13 (36.1)	12 (21.4)	9 (14.1)	<0.001
Mortality rate	15 (8.5)	1 (4.8)	1 (2.8)	6 (10.7)	7 (10.9)	0.405

Data are presented as n(%) or median (interquartile range). ICU; intensive care units

End-organ failure[8] was observed in 55 (31.1%) patients with sepsis, and the respiratory tract was the most common organ failure. A total of 15 (8.5%) patients died from the episode, of these, 14 (93.3%) had underlying diseases, and 13 of these 14 (86.7%) were suffered from nosocomial infections.

Factors associated with mortality in univariate models were immunodeficiency, CRBSI, organ failure, and nosocomial infection. Only CRBSI was independently associated with a higher risk of mortality in the multivariate model, adjusted OR 3.6 (95% CI 1.1-12.2), Table 3.

Table 3. Factors associated with mortality in pediatric patients with SIRS caused by sepsis.

Factor	Survive (N=162)	Death (N=15)	OR (95%CI)	*P*-value	Adjusted OR (95%CI)	*P*-value
Sex						
Male	87 (91.6)	8 (8.4)	1		-	-
Female	75 (91.5)	7 (8.5)	1.0 (0.2.9)	0.978	-	-
Age range						
< 2 months	20 (95.2)	1 (4.8)	1		-	-
2 months - 12 months	35 (97.2)	1 (2.8)	0.6 (0.03-9.6)	0.698	-	-
1-5 years	50 (89.3)	6 (10.7)	2.4 (0.3-21.2)	0.431	-	-
> 5 years	57 (89.1)	7 (10.9)	2.5 (0.3-21.2)	0.414	-	-

Hospital length of stay, day	14.5 (5-40)	59 (23-89)	1.0 (0.99-1.0)	0.445	-	-
Underlying diseases						
Yes	118 (89.4)	14 (10.6)	5.2 (0.7-40.9)	0.116	-	-
No	44 (97.8)	1 (2.2)	1		-	-
Immunity status						
Deficit	57 (85.1)	10 (14.9)	3.7 (1.2-11.3)	0.023*	2.6 (0.8-8.3)	0.114
Normal	105 (95.5)	5 (4.5)	1		1	-
Hemoculture results						
Positive	32 (84.2)	6 (15.8)	2.7 (0.9-8.2)	0.077	-	-
Negative	130 (93.5)	9 (6.5)	1		-	-
CRBSI						
Yes	15 (71.4)	6 (28.6)	6.5 (2.0-20.9)	0.002	3.6 (1.1-12.2)	0.036
No	147 (94.2)	9 (5.8)	1		1	-
Number of organ failure	0 (0-1)	2 (1-2)	3.6 (2.1-6.2)	<0.001	-	-
Nosocomial infection						
Yes	88 (86.3)	14 (13.7)	11.8 (1.5-91.6)	0.019	7.1 (0.9-58.4)	0.067
No	74 (98.7)	1 (1.3)	1		1	-

Data are presented as n(%) or median (interquartile range). Results are reported as odds ratios (OR) or adjusted OR with their 95% Confidence Intervals (CIs). CRBSI, catheter-related bloodstream infection

Comparing the outcomes of SIRS induced by sepsis and other causes

There was no difference in characteristics of patients with SIRS due to sepsis compared with those from other etiologies. Procalcitonin levels at baseline was measured in a small number of patients and found to be comparable between those with and without sepsis (median (IQR) 1.6 (0.6-9.5) vs 3.5 (1.6-6.9) ng/mL, respectively, p=0.557). However, patients with sepsis-induced SIRS tended to require ICU admission (27.7% vs 17.3%, p=0.130) and had a significantly higher intubation rate (38 (21.5%) vs 0, p<0.001). The length of stay (median 15 vs 8 days, p=0.234), and mortality (8.5% vs 3.8%, p=0.373) trended higher among children with sepsis-induced SIRS compared to non-sepsis causes (Table 1).

Discussion

SIRS is commonly diagnosed in clinical practice and the incidence of SIRS varies across different settings. A study in an adult emergency department reported a SIRS incidence rate of 17.8%[9], while two studies in pediatric ICU settings found higher incidence rates of SIRS between 68%-82%.[2,10] SIRS was proposed by the American College of Chest Physicians/Society of Critical Care Medicine as a criteria to help diagnose sepsis early.[11] While SIRS may have high sensitivity to diagnose sepsis, its specificity can be low.[12,13] In the present study, we found concordant evidence demonstrating that over three quarters (77.3%) of children with SIRS had sepsis. With this high sensitivity, SIRS can be considered as useful screening tool for sepsis in pediatric patients.

We found no difference between SIRS patients with and without sepsis regarding their baseline characteristic and laboratory results, including procalcitonin (PCT) levels. Although PCT has been proved as a useful marker of bacterial sepsis and a predictor of antibiotics cessation,[14] it could also be elevated in other conditions, such as post-operation,[15] which was the primary cause of non-sepsis SIRS in our study, perhaps explaining the absence of any difference. We also found that children with SIRS from sepsis had a higher rate of endotracheal intubation, and a tendency for higher ICU admission, longer hospitalization and higher mortality compared to children with SIRS without sepsis.

Similar to a previous study conducted in the Southeast Asian region,[16] the most common primary infection site was the respiratory tract. We found that the most common pathogen causing sepsis was gram-negative bacteria and a significant number of infections were nosocomial in origin, reflecting the study setting of a large tertiary hospital that provides care for patients with complicated health problems contributing to prolonged hospital stays. On the other hand, we found a substantially lower rate of viral infections compared to other report of community-acquired sepsis.[16]

We found that young infants had more severe diseases with higher rates of septic shock and ICU admission. Nonetheless, their mortality rate was lower than that of older patients. The infants had less underlying diseases and response to the treatment relatively better than did the older children. These findings were consistent with a previous study conducted in other university hospitals in Thailand.[17,18]

The mortality rate of patients with sepsis in our hospital has decreased over the last 7 years from 10.3% to 8.5%[7]. This more favorable outcome may be due to earlier recognition and more effective and timely management of sepsis. While a previous study identified age, underlying cardiovascular condition, and organ failure as predictors of hospital mortality,[19] the present study found only CRBSI as an independent predictor. In line with our finding, CRBSI was also found to be an independent risk factor for hospital mortality in ICU patients in other study, with a higher mortality rate of 8% with CRBSI.[20] CRBSI is a common source of nosocomial infection worldwide and can lead to prolonged hospitalization and increased healthcare resource utilization, potentially causing unfavorable clinical outcomes. Consequently, infectious control protocols and the central line-associated bloodstream infection prevention bundle should be implemented and strictly followed to prevent such adverse consequences.

Limitations

Our study had several limitations. This study was a single-center study conducted in a tertiary center therefore the results may not be generalizable to lower level facilities or other settings. Furthermore, the causes of SIRS and the pathogens may be different in other settings, perhaps also limiting the generalizability

Conclusion

SIRS is primarily caused by sepsis and should be employed as a tool for early diagnose to prevent mortality. As SIRS from sepsis results in poorer clinical outcomes compare to other causes, appropriate investigation and empirical management for sepsis should be delivered to children presenting with SIRS until proven otherwise. In this high-level care setting, nosocomial infections, particularly CRBSI, were responsible for half of sepsis with SIRS. Infection control measures and limiting the use of vascular catheters to only when necessary, must be underscored.

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Conflict of Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

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