

Delayed presentation is associated with serious bacterial infections among febrile infants: A prospective cohort study

Karthigha Pon Rajoo¹ MBBS, Natalia Sutiman¹ MD, Stephanie Shih² MBBS, Zi Xean Khoo^{3,5} MRCPCH, Gene Yong-Kwang Ong^{1,5,6} MRCPCH, Lena Wong⁴ BSc Hons, Rupini Piragasam⁴ BMedSc Hons, Sashikumar Ganapathy^{1,5,6} MRCPCH, Shu-Ling Chong^{1,5,6} MPH

ABSTRACT

Introduction: Febrile young infants are at risk of serious bacterial infections (SBIs), which are potentially life-threatening. This study aims to investigate the association between delayed presentation and the risk of SBIs among febrile infants.

Method: We performed a prospective cohort study on febrile infants ≤ 90 days old presenting to a Singapore paediatric emergency department (ED) between November 2017 and July 2022. We defined delayed presentation as presentation to the ED >24 hours from fever onset. We compared the proportion of SBIs in infants who had delayed presentation compared to those without, and their clinical outcomes. We also performed a multivariable logistic regression to study if delayed presentation was independently associated with the presence of SBIs.

Results: Among 1911 febrile infants analysed, 198 infants (10%) had delayed presentation. Febrile infants with delayed presentation were more likely to have SBIs (28.8% versus [vs] 16.3%, $P<0.001$). A higher proportion of infants with delayed presentation required intravenous antibiotics (64.1% vs 51.9%, $P=0.001$). After adjusting for age, sex and severity index score, delayed presentation was independently associated with the presence of SBI (adjusted odds ratio [AOR] 1.78, 95% confidence interval 1.26–2.52, $P<0.001$).

Conclusion: Febrile infants with delayed presentation are at higher risk of SBI. Frontline clinicians should take this into account when assessing febrile infants.

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Keywords: delayed presentation, emergency medicine, febrile infants, paediatrics, serious bacterial infections

CLINICAL IMPACT

What is New

- Febrile infants who present later are more likely to suffer from serious bacterial infections (SBIs) and require intravenous antibiotics.
- Even after accounting for age, sex and severity index score, delayed presentation continues to be an independent predictor of SBIs in these infants.

Clinical Implication

- When assessing febrile infants aged 0–90 days, clinicians should consider the timing of presentation as a significant factor.

complications resulting in neurocognitive deficits, hearing loss and even mortality.^{1,2} The diagnosis of SBIs remains challenging as fever may be the only symptom of SBIs in this age group.³ Clinicians need to weigh the risk of a missed or delayed diagnosis against the cost and harm of overdiagnosis and overtreatment.

Researchers have sought to derive and validate early predictors of SBI. Known clinical predictors for SBIs include high temperature, raised inflammatory markers including C-reactive protein (CRP), total white blood cell (WBC) count, absolute neutrophil count (ANC) and procalcitonin.^{4,5} The PECARN rule used procalcitonin, ANC and urinalysis to identify febrile infants aged 29–60 days at low risk of SBIs, with the aim of reducing risk and cost from unnecessary hospital admissions and lumbar punctures.⁶ The step-by-step approach uses a sequential method to identify febrile infants ≤ 90 days old at risk of SBI by considering age, clinical appearance, ANC, CPR and procalcitonin and

INTRODUCTION

Young infants ≤ 90 days old are at risk of serious bacterial infections (SBIs) due to their immature immune systems and may develop severe

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¹ Department of Children's Emergency, KK Women's and Children's Hospital, Singapore

² Barts and the London School of Medicine and Dentistry, Queen Mary University of London

³ Department of Paediatric Medicine, KK Women's and Children's Hospital, Singapore

⁴ KK Research Centre, KK Women's and Children's Hospital, Singapore

⁵ SingHealth-Duke NUS Paediatrics Academic Clinical Programme, Duke-NUS Medical School, Singapore

⁶ SingHealth-Duke NUS Emergency Medicine Academic Clinical Programme, Duke-NUS Medical School, Singapore

Correspondence: Dr Chong Shu Ling, Department of Children's Emergency, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: chong.shu-ling@kkh.com.sg

urinalysis.⁷ External validation of these prediction rules has demonstrated variable performance in different populations ≤ 90 days old.^{5,8}

Previous studies have explored temperature as a predictor of SBIs. High temperatures are associated with the presence of SBIs,⁹ and this has been validated in Singapore.⁴ A secondary analysis of a multicentre prospective study reported a lower risk of SBIs in infants who had a history of fever but were afebrile on arrival to the emergency department (ED), as compared to infants who were febrile in ED (relative risk 0.68, 95% confidence interval [CI] 0.56–0.84).¹⁰ In a study among children 3–36 months old, it was reported that every 1-hour increase in the duration of fever resulted in an increased odds of 1.01 for occult bacteraemia (adjusted odds ratio [AOR] 1.01; 95% CI 1.00–1.03, $P=0.01$), after adjusting for CRP and ANC.¹¹ However, among young infants ≤ 90 days old, there is limited literature on the association between the delayed presentation and the presence of SBIs.¹²

We aimed to investigate if delayed presentation (defined as arrival in the ED more than 24 hours after the onset of fever) is associated with the presence of SBIs among febrile infants ≤ 90 days of age. We also sought to compare the clinical characteristics of febrile infants with delayed presentation, with those who did not have delayed presentation.

METHOD

Study setting and design

We performed a prospective study among infants ≤ 90 days in the paediatric ED of KK Women's and Children's Hospital (KKH) in Singapore between November 2017 and July 2022. KKH is 1 of 2 paediatric tertiary centres in Singapore, and the ED sees about 150,000 children a year. Institutional review board (IRB) approvals were obtained for the conduct of this study. Between November 2017 and December 2020, patients were recruited as part of an ongoing study that sought to understand heart rate variability among febrile young infants (IRB: 2022/2457). From January 2021 to July 2022, we obtained IRB approval for the consecutive recruitment of all eligible febrile infants (IRB: 2017/2680).

Patient population

We recruited infants ≤ 90 days old with an axillary or rectal temperature of ≥ 38.0 °C. We excluded infants with than 35 weeks gestation, since these preterm infants would constitute a higher-risk population. These infants have a lower threshold for investigations and interventions in view of

their prematurity. In KKH, all febrile infants ≤ 90 days old are hospitalised. Neonates < 28 days old usually undergo a full septic workup that includes blood culture, urinalysis and urine culture, as well as cerebrospinal fluid (CSF) analysis and culture. Infants between 28 and 90 days old undergo further risk stratification and may receive a more limited workup depending on physician discretion. All infants are monitored until they are afebrile for 24 hours before discharge.

Study variables

The following were obtained at ED triage: temperature, heart rate and severity index score (SIS). Nurses obtained the temperature at triage, with the infant in a single layer of wrapping. Fever is defined as an axillary or rectal temperature of ≥ 38.0 °C measured at triage. Heart rate was obtained from pulse oximetry. Where there was interference with movement, the heart rate was obtained manually. SIS is a composite score comprising respiratory effort, colour, activity, temperature and play, with a score of 10 (not very sick), 8–9 (moderately sick) and ≤ 7 (very sick).¹³ We defined delayed presentation as infants who presented more than 24 hours after the onset of fever, as reported by parents. Laboratory results included WBC, ANC, haemoglobin, platelets, CRP and procalcitonin. We also recorded interventions such as fluid bolus and intravenous antibiotics.

Outcome measures

SBIs are defined as bacteraemia, urinary tract infections or bacterial meningitis.¹⁴ Invasive bacterial infection (IBI) is defined as bacteraemia and/or bacterial meningitis.⁸ UTI was defined as presence of a single bacteria of $> 100,000$ colony-forming unit (CFU)/mL in a clean midstream sample or $\geq 50,000$ CFU/mL in a catheterised sample or 10,000–50,000 CFU/mL in a catheterised sample with an abnormal urinalysis (positive for leukocyte esterase or nitrite).¹⁵ Bacteraemia was defined as growth of a single bacterial pathogen in blood, excluding growth of contaminants (e.g. coagulase-negative *Staphylococcus* determined as a priori).¹⁶ Bacterial meningitis was defined as CSF leucocytes > 5 cells/uL and positive bacterial culture.⁸ We also documented the hospital length of stay (in days).

Statistical analysis

Categorical variables were presented with frequencies and proportions, while continuous variables were presented using mean or median, with standard deviation (SD) or interquartile range (IQR), depending on whether the data were parametric. We compared the clinical presentation,

laboratory findings, management variables between infants with delayed presentation compared to those without. Categorical variables were analysed using the chi-square test, while continuous variables were analysed using the t-test or Wilcoxon rank-sum test, depending on normality.

We also performed a multivariable logistic regression to investigate if delayed presentation was independently associated with the presence of SBI. Variables were chosen based on their univariate significance as well as known risk factors in the literature and clinical discretion. Known predictors from the literature and earlier studies that we had performed in the febrile population were age, male sex and SIS.^{5,6,12} Hence, we took these into account when performing the multivariable regression. We presented the unadjusted ORs and AORs, together with their *P* values. Statistical significance was taken at *P*<0.05. We did not perform multiple imputation for missing data unless there were more than 10% missing in the analysed variables.

RESULTS

Among 1912 patients analysed, 198 infants (10.4%) had delayed presentation (Fig. 1). The baseline demographics, clinical characteristics and outcomes are described in Table 1. Febrile infants with delayed presentation were significantly older compared to those without delayed presentation (mean 50 days SD 24.6 vs 38 days, SD 27.6 *P*<0.001). The mean temperature (38.6°C SD 0.6°C vs 38.4 °C SD 0.6°C, *P*<0.001) and mean heart rate (168/min SD 19.5 vs 161/min, SD 20.4, *P*<0.001) were significantly higher for infants with delayed presentation compared to those without.

When comparing the group with delayed presentation to the group without, the median CRP (10.3 mg/L, IQR 0.6–47.7 vs 1.5 mg/L, IQR 0.5–8.1, *P*<0.001), median WBC (12.1 x 10⁹/L, IQR 9.1–15.9 vs 11.1 x 10⁹/L, IQR 7.5–14.5, *P*=0.001) and median procalcitonin (0.1 ug/L, IQR 0.07–0.35 vs 0.08 ug/L, IQR 0.05–0.15, *P*<0.001) were higher (Table 2). The ANC for both groups was comparable (median 4.6 x 10⁹/L, IQR 2.4–7.6 vs 3.9 x 10⁹/L, IQR 2.2–6.5, *P*=0.33).

Fig. 1. Classification of recruited patients and incidence of serious bacterial infections (SBIs).

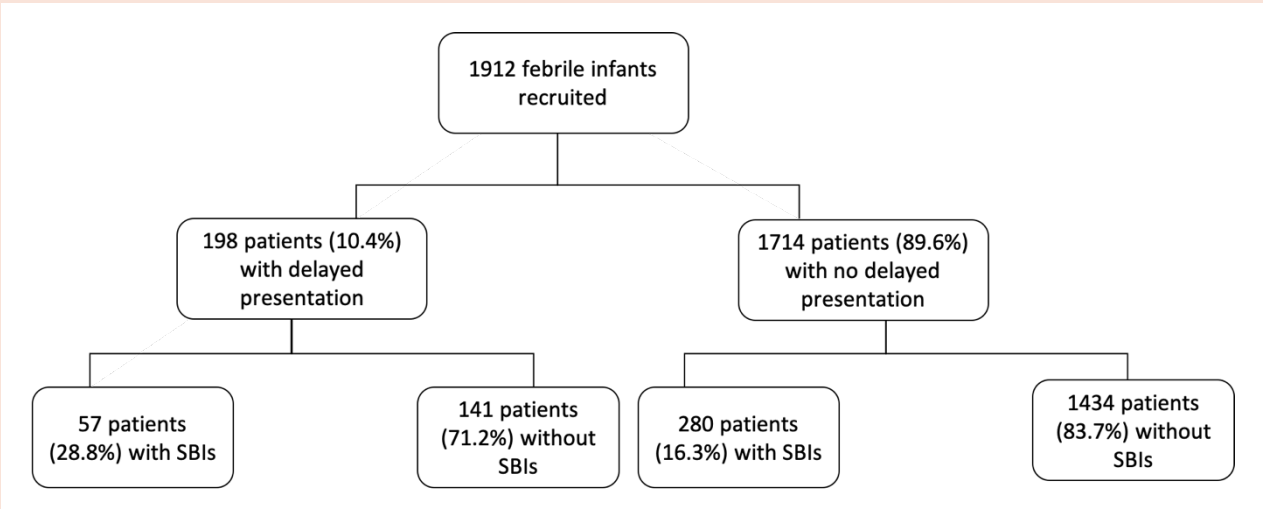


Table 1. Baseline demographics and clinical characteristics of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	P value
Age in days, mean ± SD	50 ± 24	38 ± 28	<0.001
Male sex, no. (%)	113 (57.1)	981 (57.2)	0.965
Temperature in °C, mean ± SD	38.6 ± 0.6	38.4 ± 0.6	<0.001
Heart rate/min, mean ± SD	168 ± 20	161 ± 20	<0.001
SIS, median (IQR)	9 (8–9)	9 (9–10)	<0.001

IQR: interquartile range; SD: standard deviation; SIS: severity index score

Table 2. Laboratory results of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	P value
Haemoglobin in g/dL	11.3 (10.3–12.9)	12.1 (10.8–15.8)	<0.001
Total white cell count x 10 ⁹ /L	12.1 (9.1–15.9)	11.1 (7.5–14.5)	0.001
Absolute neutrophil count x 10 ⁹ /L	4.6 (2.4–7.6)	3.9 (2.2–6.5)	0.33
Platelets x 10 ⁹ /L	419 (324–509)	396 (323–484)	0.106
C-reactive protein in mg/L	10.3 (0.6–47.7)	1.5 (0.5–8.1)	<0.001
Procalcitonin in ug/L	0.10 (0.07–0.35)	0.08 (0.05–0.15)	<0.001

All values are in median (interquartile range).

There were 337 infants with SBIs, among whom 37 (11.0%) had meningitis or bacteraemia (defined as IBIs) and 300 (89.0%) were UTIs (Table 3). Infants with delayed presentation were more likely to have SBIs in general (28.8% vs 16.3%, $P<0.001$), specifically UTIs (25.8% vs 14.5%, $P<0.001$) and require intravenous antibiotics (64.1% vs 51.9%, $P=0.001$), compared to those without delayed presentation. IBI rates (3.0% vs 1.8%, $P=0.237$) and requirement for fluid bolus (6.1% vs 3.5%, $P=0.073$) were comparable between the 2 groups. We did not find clinically important differences in the median length of hospital stay.

In the multivariable logistic regression (Table 4), after adjusting for age, sex and SIS, we found that delayed presentation was independently associated with the presence of SBIs (AOR 1.78 95% CI 1.26–2.52, $P<0.001$). Male sex and low SIS were also independently associated with the presence of SBIs (AOR 2.47 95% CI 1.89–3.23, $P<0.001$ and AOR 0.66 95% CI 0.57–0.77, $P<0.001$). After adjustment, delayed presentation was an independent predictor for UTI (AOR 1.75 95% CI 1.22–2.51, $P=0.002$) but not for IBI (AOR 1.63 95% CI 0.65–4.08, $P=0.298$) (Supplementary Tables S1 and S2).

Table 3. Clinical outcomes of infants with delayed presentation compared to those without delayed presentation.

Variables	Infants with delayed presentation (n=198)	Infants with no delayed presentation (n=1714)	P value
SBI, no. (%)	57 (28.8)	280 (16.3)	<0.001
Urinary tract infections, no. (%)	51 (25.8)	249 (14.5)	<0.001
Invasive bacterial infections, no. (%)	6 (3.0)	31 (1.8)	0.237
Antibiotics, no. (%)	127 (64.1)	890 (51.9)	0.001
Fluid bolus, no. (%)	12 (6.1)	60 (3.5)	0.073
Length of hospital stay in days, median (IQR)	3.00 (3–4)	3.00 (2–4)	0.009

IQR: interquartile range; SBI: serious bacterial infection
Invasive bacterial infections = bacteraemia and meningitis

Table 4. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in febrile infants.

Variables	Unadjusted odds ratio (95% CI)	Unadjusted P value	Adjusted odds ratio (95% CI)	Adjusted P value
Age in days	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.054
Male sex	2.45 (1.88–3.18)	<0.001	2.47 (1.89–3.23)	<0.001
Severity index score	0.63 (0.54–0.72)	<0.001	0.66 (0.57–0.77)	<0.001
Delayed presentation	2.07 (1.48–2.89)	<0.001	1.78 (1.26–2.52)	0.001

CI: confidence interval
Bold text represents the variable of interest.

We also compared the prevalence of SBI between 2 subgroups in our study population—neonates and infants between 29–90 days old. The prevalence of SBI in neonates was 13%; this was 20.6% in infants between 28–90 days old. On performing a sensitivity analysis, we found that delayed presentation was independently associated with SBI among neonates (AOR 2.50, 95% CI 1.13–5.49, $P=0.023$) and in older infants between 29–90 days old (AOR 1.64, 95% CI 1.12–2.41, $P=0.012$) (Supplementary Tables S3 and S4).

DISCUSSION

In this prospective cohort study among febrile infants ≤ 90 days old, we found that febrile infants with delayed presentation (>24 hours from fever onset) were more likely to have SBIs (AOR 1.78 95% CI 1.26–2.52, $P<0.001$) after adjusting for age, sex and SIS, and were more likely to require intravenous antibiotics (64.1% vs 51.9%, $P=0.001$). Further analysis showed that delayed presentation is associated with increased risk of SBI both in neonates and older infants between 29–90 days old.

Febrile infants are at risk of SBIs, with a reported prevalence of 9–25%.^{8,17} Early identification enables the timely initiation of antibiotics which reduces mortality, and shortens the duration of hospitalisation.^{18,19} Delayed presentation potentially leads to delayed investigations and administration of empirical antibiotics, resulting in a higher risk of sepsis and death.^{19–21} Our findings highlight the importance of vigilance, especially among febrile infants who present >24 hours after fever onset. These infants require a robust assessment with consideration for early antibiotics.

Although the specific association between delayed presentation to the ED and risk of SBI has not been evaluated, several other studies have reported the relationship between duration of fever and SBIs in febrile children.¹² Some studies among patients up to 36 months old report that a longer duration of fever was associated with an increased risk of SBI.^{22,23} However, in a systematic review, the duration of fever was not significantly associated with SBIs among children 1 month–18 years old presenting to ambulatory care settings in developed countries.²⁴ Similarly, another systematic review done among children between 2 months and 6 years old showed that fever duration was inconclusive for SBI.²⁵ We recognise that the patient populations in these systematic reviews included children, which differ from ours. We chose to focus on the young infant population ≤ 90 days old, who are at high risk of SBIs due to their immature

immune system. This group warrants close monitoring and prioritisation of investigations and early management.

Additionally, it is not presently known whether the significance of this association differs depending on the different types of SBIs. Young children with fever lasting >48 hours have been reported to have a higher likelihood of UTIs.²⁶ We did find that infants with delayed presentations were more likely to have an underlying UTI. There were smaller numbers with IBI (i.e. both meningitis and bacteraemia) in our population. Despite not achieving statistical significance, we did find that the proportion of those with IBIs was almost double in the group with delayed presentation compared to those without delayed presentation. In a prospective cohort study conducted in 9 paediatric emergency centres, the duration of fever in young children with and without bacteraemia were comparable.^{27,28} We postulate that the strength of association between delayed presentation and disease may differ between different types of SBIs due in part to the different rate of clinical progression of these conditions. Future larger prospective studies should consider investigating this association stratified by different types of SBIs.

We recognise the limitations of this study. First, while the prospective nature of this study allowed for variables determined a priori to be captured, this was a single-centre study and the findings require external validation. Second, in view of differences in clinical practices among physicians in the management of febrile infants, not all infants recruited to the study had the complete diagnostic tests performed, which makes it possible that some SBIs were missed. However, we believe that this number is small because it is our institutional practice that all infants are monitored in the hospital until afebrile for at least 24 hours. Furthermore, we did not account for any treatments received by the infant prior to the emergency visit. We did not have the necessary information to investigate socioeconomic status of these families and the association with delayed presentation, which could potentially impact health education policies. Future studies should investigate socio-economic status in SBI epidemiology and outcomes. Third, as part of routine clinical practice, ED nurses usually measure axillary temperature because it is less invasive than rectal temperature. However studies have shown that rectal temperature is more accurate in infants.^{29,30} Finally, the number of infants with IBIs was small, limiting our conclusions on delayed presentation in this subpopulation.

CONCLUSION

In conclusion, febrile infants with delayed presentation >24 hours from fever onset are at higher risk of SBIs. As such, clinicians should take this into account when assessing febrile infants. In addition, future studies should evaluate the association between delayed presentation and specific types of SBIs. Such findings have potential for translation into clinical risk stratification protocols in the ED.

Supplementary materials

Table S1. Multivariable logistic regression for delayed presentation in predicting the presence of urinary tract infections among febrile infants.

Table S2. Multivariable logistic regression for delayed presentation in predicting the presence of invasive bacterial infections among febrile infants.

Table S3. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in neonates less than 28 days old.

Table S4. Multivariable logistic regression for delayed presentation in predicting the presence of serious bacterial infections in infants 29 days to 60 days old.

Author contributions

KPR, NS and S-LC made substantial contributions to the conception and design of the work, the analysis and interpretation, drafted the initial manuscript and revised it critically for important intellectual content. SS contributed in the conception and design of the work, data interpretation and drafting of the initial manuscript. SG, ZXK and GY-KO contributed in the analysis, interpretation of data for the work, revising it critically for important intellectual content. LW and RP acquired and interpreted the data, and revised the draft for important intellectual content. All authors agree for the final approval of the version to be published and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors have no conflict of interest to declare.

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