Original Article

Risk Stratification Of Signs Of Possible Serious Bacterial Infection For Prediction Of Mortality Among Young Infants

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ABSTRACT

Objective: Possible serious bacterial infection (PSBI) is one of the leading causes of infant mortality. Based on WHO multi-centric study, signs of PSBI are categorized into: signs of clinical severe infection (CSI) and signs of critical illness (CI). Assessment of signs of PSBI helps to divide infants into risk groups for appropriate management and prognostication. This study aimed to assess risk stratification of signs of PSBI among young infants **(**0- 59 days of age) by correlating signs of PSBI with mortality. **Methods**: In this hospital-based prospective cohort study, 220 young infants with signs of PSBI were recruited. Infants were categorized into two: those with signs of CSI and those with signs of CI. Correlation of each sign of PSBI was done with mortality. Time to death was assessed by using the Kaplan Meier survival analysis. **Results**: 220 infants were analyzed for outcomes. Signs of CSI including fever, fast breathing, poor feeding, and movement only on stimulation had a low fatality rate; however low body temperature and severe chest pain was associated with high mortality of 20% and 9%, respectively. CI signs – convulsion, no movement at all, and no feeding at all were associated with high death rates of 14%, 63.7%, and 47.4% respectively. The majority of deaths were occurred within 48 hours of presentation. **Conclusions**: Mortality was high in infants with low body temperature, chest pain, or any sign of CI. Risk stratification based on clinical signs could help prioritize infants in need for urgent intervention and thus decrease infant mortality.

Key words: Infant, sepsis, convulsions, mortality.

Infant Mortality Rate (IMR), defined as the number of deaths for every 1000 live births occurring before the first birthday, is a pivotal indicator of the healthcare status of a population and the welfare of a country. Worldwide, there has been an overall reduction in the global IMR from 64.5 to 28.2 between 1990 and 2019 [1]. India still trails behind most of the countries with an IMR in 2021 being 28.7, a drop of 3.61% from 2020[2]. The neonatal mortality rate in India, similarly underwent a significant reduction from 57.4 in 1990 to 21.7 in 2019[3]. Various studies indicate that among under 5 population, the neonatal group contributes to maximum mortality and with increasing age, there is a steady decrease in mortality. In 2019, among children younger than 5 years, the leading causes of death were complications due to prematurity(17.7%), lower respiratory infections(13.9%), and intrapartum-related events(11.6%), altogether constituting 43.2% of under-5 deaths[4]. Prematurity, low birth weight, perinatal complications, and sepsis constitute nearly 80% of all neonatal mortalities with slight deviations according to the region and neonatal period[5]. Globally, sepsis stands out as one of the major causes of mortality among infants [6]. Sepsis, by definition is a life-threatening organ dysfunction caused by a dysregulated host response to infection [7]. Various infections could predispose to such organ dysfunction and include septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection[8]. The time of the onset of symptoms helps us classify sepsis into early onset sepsis(EOS) and late onset sepsis(LOS); EOS being maternal-fetal infection acquired before or during delivery while LOS is an infection horizontally acquired in healthcare or community settings after birth[9].

Early identification of risk factors for neonatal sepsis can reduce infant morbidity and mortality. Non-specific symptoms and signs, scarcity of appropriately trained health

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workers, improper transport, limited access to healthcare, and lack of awareness in communities lead to delays in seeking appropriate medical attention resulting in high mortality due to infections. By and large, 99% of these deaths occur in low- and middle-income countries[10]. Contributing to one-third of neonatal deaths, infections account for a higher proportion of neonatal mortality in India as compared to global averages[11]. In both hospital and community settings, the case fatality rates from neonatal infections remain uncomfortably high.

WHO conducted a multicentric young infant study and derived a model approach for community-based identification of clinical signs that predict serious illness and hence need for immediate hospitalisation. Based on the above study, signs of possible serious bacterial infection (PSBI) were recommended for assessment. These included fast breathing (respiratory rate ≥ 60 breaths/minute), severe chest in-drawing, fever (temperature ≥ 38 °C), hypothermia (temperature < 35.5 °C), movement only on stimulation, feeding poorly, not feeding at all, no movement at all, and, convulsions[12]. WHO recommends that young infants up to 59 days of age with PSBI should be given injectable antibiotics at appropriate healthcare facilities and when referral to hospital is not feasible, these infants, expect for those who are critically ill, can be managed on an outpatient basis with injectable gentamicin for 2 days followed by oral amoxicillin for 5 days or oral amoxicillin for 7 days[13].

Based on the WHO recommendations which included outpatient management of cases where referrals are not possible, the African Neonatal Sepsis Trial (AFRINEST) multicentric study was conducted(unpublished). In this study, signs of sepsis were classified into signs of clinical severe infection (CSI) and signs of critical illness (CI)[12]. PSBI signs were further stratified into low mortality risk and high mortality risk signs. It was seen that mortality in infants with low-risk signs was higher in hospital compared to outpatient management, thus generating a possibility of outpatient/ community-based management of these infants.

If the signs of PSBI can be stratified in Indian settings, it would be helpful in formulating health care policy where the possibility of community-based management of these infants can be explored. This would prove crucial in reducing the burden of in hospital patients in the resource limited low middle income countries (LMICs). This study aimed to assess risk stratification of signs of possible serious bacterial infection (PSBI) among young infants **(**0- 59 days of age **)** admitted to a tertiary care hospital by correlating signs of PSBI (CSI and CI) with mortality, and, with time to death after presenting to hospital.

MATERIALS AND METHODS

This was a prospective cohort study, conducted in the Department of Paediatrics VMMC and Safdarjung Hospital, New Delhi from January 2021 to June 2022. A written informed consent was taken from the parents before enrolling their infants. All young infants 0-59 days of life presenting to the pediatric emergency with one or more signs of PSBI, were included in the study. The signs of PSBI were further classified into signs of CSI which included (i)fast breathing; (ii)movement only when stimulated; (iii) not feeding well on observation; (iv) temperature ≥38 °C; (v) temperature <35.5 °C and; (vi) severe chest in-drawing; and signs of CI which included (i) no movement at all; (ii) convulsions and (iii) unable to feed at all. These signs were identified and monitored by the attending clinical team. Infants with major congenital malformation, weight at admission < 1500 gm, and those requiring surgery/exchange transfusion were excluded from the study.

Sample size: Considering the infant mortality rate in pediatric unit of Safdarjung Hospital, we calculated a sample size of 250 young infants to be included in the study.

Course in hospital: Based on the clinical signs and symptoms, the study infants were examined by the clinical team and treated by standard unit protocols**.** Laboratory investigations were sent which included Complete blx`ood count (CBC), C-reactive protein (CRP), blood culture, chest X-ray in cases of respiratory distress, urine microscopy/cultures and CSF examination (Late onset sepsis in neonate / features of meningitis on history or examination beyond neonatal period) including cytology, biochemistry, and culture. Intravenous antibiotics and supportive management in the form of respiratory support (oxygen therapy/CPAP/ventilation) as indicated by clinical condition were given. Blood product transfusion as per the paediatric transfusion guidelines for PRBC, FFP, and platelet were provided.

The point of assessment of outcomes was at the time of death or discharge [**Figure 1**]. Discharge criteria, all of which must have been fulfilled included completion of intravenous antibiotics, resolution of underlying condition, accepting of full oral feeds/breastfeeds and breathing room air for past 48 hours.

Our study used the principles of the Declaration of Helsinki (2008). The study was approved by the Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi institutes' ethics committee (date: October 30, 2019; serial number: 214). Informed consent was obtained from the parents of the infants who agreed for them to participate in the study.

Statistical analysis: The data was entered into a pre-designed pro forma in Microsoft Office Excel spreadsheet (Microsoft

Corporation, Redmond, WA, USA) and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0(IBM Corp., Armonk, NY, USA). Categorical variables were presented in number and percentage (%) and continuous variables were presented as median ± IQR. Categorical variables were compared using the Chi-Square test or Fisher's exact test. Time to mortality was analysed using the Kaplan-Meier survival analysis. A p-value of <0.05 was considered statistically significant.

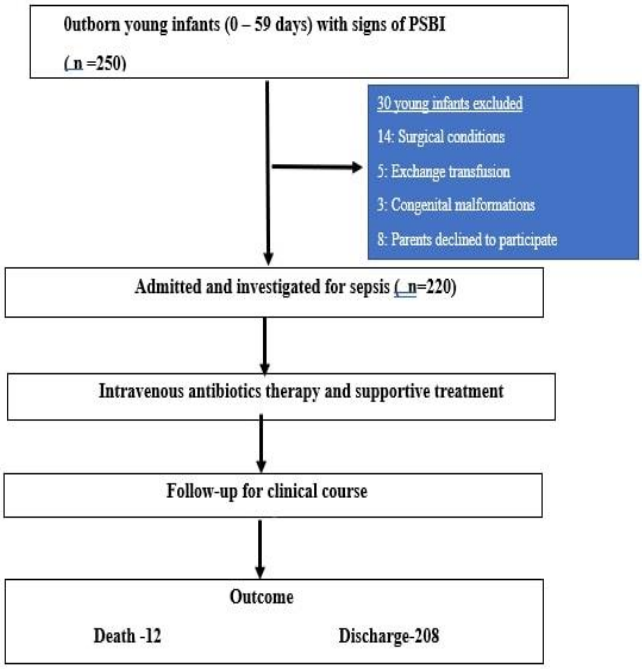


Figure 1: Flow of study

RESULTS

Out of 250 young infants admitted with signs of PSBI, 30 were excluded for various reasons(Figure 1) and 220 infants were analyzed for outcomes. Of the 220 young infants enrolled, 113 (51%) were female and 107 (49%) were male. Age stratification, survival, and death distribution are presented in [**Table 1]**. We did not find any significant difference of different age strata with mortality in infants less than 2 months of age. Similarly for sex, we did not find any statistically significant association with mortality; 6 out of 113 female infants (5.3%) and 6 out of 107 male infants died (5.3%),p-value>0.05. **Risk stratification of signs of CSI for prediction of mortality:** Of all signs of CSI, only low body temperature was significantly correlated with mortality in young infants **[Table 2].** No statistically significant difference was seen between other signs of CSI, including fast breathing, severe chest pain, fever (temperature ≥ 38 °C), poor feeding or movement only on stimulation, and mortality. Case fatalities in signs of CSI were: fever:3.5% (5 out of 143 infants), fast breathing:4.1% (3 out of 73 infants), severe chest indrawing-9.1% (3 out of 33 infants), poor feeding: 2.1% (2 out of 92 infants), movement only on stimulation:2.5% (1 out of 40 infants), and low body temperature:20% (3 out of 15 infants).

Risk stratification of signs of CI for prediction of mortality: out of 220 infants, 70 infants presented with signs of CI and all three signs showed a statistically significant

Table 1: Distribution of age of study subjects [n=220]

Age(days)	Total	n (%)	Survived, n (%)	Mortality, n (%)	p-value
0-7	154	77 (35)	73 (94.8)	4 (5.2)	>0.05
8-28	174	87 (40)	82 (94.2)	5 (5.8)	
29-59	112	56 (25)	53 (94.6)	3 (5.4)	

Table 2: Risk stratification of signs of clinically severe infection (CSI) for prediction of mortality in young infants(n=220)

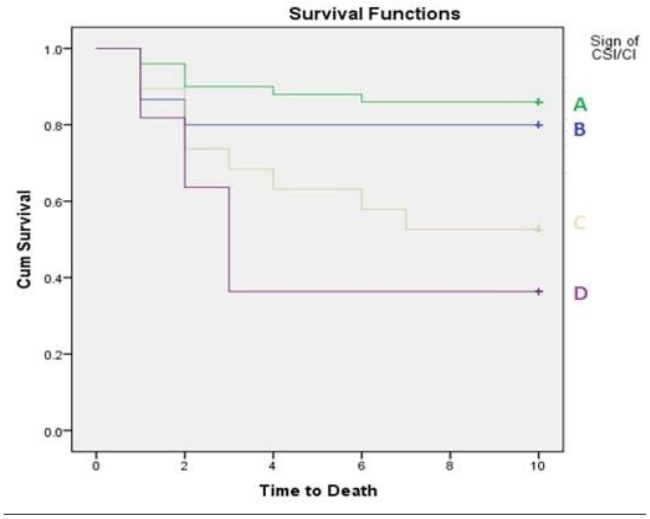
Sign of Clinical severe infection	Distribution	Total	Survived, n (%)	Mortality, n (%)	P value
Fever	Present	143	138 (96.5)	5 (3.5)	0.081
	Absent	73	70 (95.9)	3 (4.1)	
Fast breathing	Present	73	70 (95.9)	3 (4.1)	0.536
	Absent	147	138 (93.9)	9 (6.1)	
Severe chest indrawing	Present	33	30 (90.9)	3 (9.1)	0.318
	Absent	187	178 (95.2)	9 (4.8)	
Movement only on stimulation	Present	40	39 (97.5)	1 (2.5)	0.363
	Absent	180	169 (93.9)	11 (6.1)	
Poor feeding	Present	92	90 (97.8)	2 (2.2)	0.069
	Absent	128	118 (92.2)	10 (7.8)	
Low body temperature	Present	15	12 (80)	3 (20)	0.01
	Absent	205	196 (95.6)	9 (4.4)	

difference in mortality among infants in whom these signs were present compared with those infants in whom these signs were absent **[Table 3].** Case fatality rates were: convulsions:14% (7 out of 50 infants), no feeding at all: 47.4% (9 out of 19 infants) and no movement at all: 63.7% (7 out of 11 infants).

Table 3: Risk stratification of signs of critical illness(CI) for prediction of mortality in young infants(n=70)

Critical illness sign	Distribution	Total	Survived, n (%)	Mortality, n (%)	P value
Convulsions	Present	50	43 (86)	7 (14)	0.007
	Absent	170	165 (97.1)	5 (2.9)	
No feeding at all	Present	19	10 (52.6)	9 (47.4)	<0.001
	Absent	201	198 (98.5)	3 (1.5)	
No movement at all	Present	11	4 (36.4)	7 (63.6)	<0.001
	Absent	209	204 (97.6)	5 (2.4)	

Risk stratification of low body temperature and signs of critical illness for prediction of time to death: Our study showed that infants with one of the signs of CSI (low body temperature) or any sign of CI had significantly higher mortality when compared to other signs of CSI. The time to death from the time of admission to hospital was analyzed using the Kaplan Meier survival analysis. Median time of death was 48- 32 hours. Most of the deaths occurred within 48 hours of admission **[Figure 2]**.



CI: Critical illness; CSI: Clinical severe infection; A: low body temperature; B: convulsions; C: not feeding at all; D: no movement all.

Figure 2: Time to death using the Kaplan Meier survival plot.

DISCUSSION

PSBI is a major contributor to young infant mortality. A clear understanding of the signs of PSBI can help drive the development of a risk prediction model, which can further lead to the early identification of high-risk infants. This will also help triage resources to improve health outcomes and health care efficiency. Secondly, expanding our understanding of clinical risk factors for mortality in this age group could highlight key diagnostic approaches and research gaps in these areas.

To the best of our knowledge, the AFRINEST trial was the only study that showed the correlation between signs of PSBI with mortality. Although unpublished, the secondary observational analysis of this study have been published[13, 14]. In the AFRINEST study, overall case fatality rate was 5.4%. A Study done by Anna C Seale et al, which made the first estimate of neonatal mortality caused by PSBI, by sex, and– region showed that the mortality rate among young infants in the region of sub-Saharan Africa, South Asia, and Latin America, was 10%[10]. However, in a cohort study conducted by Marie E Wang et al in resource-limited 20 rural primary health centres(PHC), a high mortality rate of 23% was seen [15].

Our study aimed at stratifying each sign of PSBI for prediction of mortality risk, which can help in the prompt categorisation of an infant into high or low risk for mortality. This will ensure early initiation of antibiotics and other supportive interventions, thereby reducing the burden of mortality and morbidity in young infants. The present study showed that young infants presenting to the outpatient unit with signs of CSI, i.e. fever, fast breathing, poor feeding, and movement only on stimulation, had a lower-case fatality-rates of 3.6%, 4.1%, 2.1%, and 2.5%, respectively. This was in accordance with the results of the AFRINEST trial which showed that fever, fast breathing, poor feeding and movement only on stimulation had lower case fatality rates of 0.8%, 1.9%, 4%, and 3.2%, respectively. Our study also showed that severe chest pain and low body temperature had a higher case fatality rate of 9% and 20% respectively. The figures are noticeably high and these signs should have been prioritized and given equal importance to signs of CI and managed urgently in hospital settings.

All infants with signs of CI, as shown in our study had a higher risk of death when compared to infants with signs of CSI; being 14%, 47.4%, and 63.7% in infants presenting with convulsions, no feeding at all and no movement at all, respectively. This was significantly higher than the AFRINEST study in which the mortalities in similar order were 11.3, 22.9% and 25%, respectively As a tertiary care center, our study may have a higher case fatality rate because

the majority of referred cases are sick infants who cannot be treated at the primary health care level. Also, the problem is further compounded by delayed or poor identification of danger signs at home or at a primary health care–facilities contributing to delays in the provision of timely medical care.

The present study also determined the relationship between time to mortality and signs of PSBI. Our study showed maximum mortality within 48 hours of hospital admission, which signifies the importance of golden hour management. Similar results were also seen in the AFRINEST trial, where most of the mortality was seen within 48 hours. None of the infants in our study died after 7 days of admission to hospital.

The main limitation of the study was that it was not conducted in a community setting where the application of risk stratification could have been most beneficial. Being a single tertiary care center study, the patient profile was different than that seen at the primary health care level. Nevertheless, with our large sample and prospective design, we could elucidate a pivotal correlation of signs of PSBI with mortality which could very well be applied in basic health care settings and would help priortize care and referral of those infants who are at higher risk of mortality.

CONCLUSION

This study supports the critical importance of early recognition of signs of PSBI and triaging young infants by the severity of clinical signs. Rapid mobilization from referring centers after initial stabilization in hospital management and prioritizing infants with signs of CI for aggressive management will make a significant impact in accomplishment of sustainable development goals of reducing child mortality.

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