RESEARCH PAPER

Predictors of Mortality in Neonatal Pneumonia: An INCLEN Childhood Pneumonia Study

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Background: Neonatal pneumonia contributes significantly to mortality due to pneumonia in the under-five age group, but the predictors of mortality are largely unknown.

Objective: To evaluate the clinical and microbiological characteristics and other risk factors that predict mortality in neonates admitted with pneumonia in tertiary care centres.

Study design: Prospective observational cohort study.

Participants: Term and preterm (32 weeks to 36 $^{6/7}$ weeks) neonates (<28 days of life) admitted with clinical and radiological features suggestive of pneumonia.

Intervention: Baseline sociodemographic data, clinical details, blood culture and nasopharyngeal swabs for virologic assay (RT PCR for RSV, Influenza) were collected at admission and the neonates were observed throughout their hospital stay.

Outcome: The primary outcome was predictors of mortality in neonatal pneumonia.

Results: Five hundred neonates were enrolled in the study. Out of 476 neonates with known outcomes, 39 (8.2%) died. On multivariate analysis, blood culture positive sepsis was independently associated with mortality (adjusted OR 2.51, 95% CI1.23 to 5.11; *P*-0.01).

Conclusion: Neonates with blood culture positive pneumonia positive are at a higher risk of death.

Key words: *Burden, Early onset sepsis, Outcome, Risk Factors*.

With a mortality rate of 37/1000 live births, India ranks among the top five nations with high under five mortality rates. Neonatal mortality, comprising 60% of under-five mortality, is markedly higher than that in any high-income group country [1]. Neonatal sepsis, the third most common cause of neonatal deaths, has a significant impact on long term neurodevelopment. Neonatal pneumonia alone accounts for 2% (0.136 million) of under-five mortality in children in the world [2].

Though the incidence of neonatal sepsis among NICU admissions in our country is reported to be 14.3%, the occurrence of neonatal pneumonia and the factors predicting mortality are not well studied [3-7]. Ventilator associated pneumonia is common among preterm, low birth weight or mechanically ventilated newborns [7]. In this study, we evaluate the clinical and microbiological characteristics and other risk factors that predict mortality in term and preterm (32 to 36 $^{6/7}$ weeks) neonates admitted with pneumonia, in tertiary care public sector pediatric hospitals, catering predominantly to outborn neonates.

METHODS

This multi-centre, prospective, cohort study, conducted in two tertiary level public sector hospitals, included neonates having tachypnea, respiratory distress (chest retractions/ grunting) and evidence of pneumonia on chest *X*-ray [8]. Neonates having meconium aspiration syndrome, or respiratory distress developing within first 2 hours of life and improving within 12 hours of life or those with major congenital malformations or those admitted for >24 hours in another hospital or received antibiotics prior to admission, were excluded. Nodular or coarse, patchy non-homogenous infiltrates, air broncho-gram, lobar, multi lobar or segmental consolidation were considered as radiological evidence of pneumonia. Eligible infants were enrolled after obtaining consent from either parent. Blood culture and nasopharyngeal aspirates was taken at admission and case details, clinical course and the outcome data were recorded in a predesigned proforma. The clinical staff were trained to interpret *X*-rays and the diagnosis was made by the resident involved in study, was confirmed by a

consultant, and the neonates were managed as per standard treatment guidelines [9]. Echocardiography was done only when clinically indicated.

The primary outcome was predictors of mortality in neonatal pneumonia. Predictors evaluated included socio-demographic factors, maternal age, maternal fever, parity, mode of delivery, the clinical features at admission [10] and during the course of hospitalization as well as microbiological characteristics of the isolates. The secondary outcomes included overall blood culture positivity rate in neonatal pneumonia, the distribution of microbiological causes, the need for higher respiratory support and complications of pneumonia.

To ensure quality, the microbiological samples were processed at a NABL accredited laboratory with an active external quality assessment program. Apart from this, the unusual bacterial organisms and fungal isolates were confirmed using MALDI TOF assay at an another NABL accredited laboratory. Further, interlab comparison of 10% of all positive and negative viral isolates were done. All data collected were cross-verified by the site investigators periodically.

Assuming a 10% prevalence of any of the predictors, an odds ratio of 2.5 for mortality and a mortality rate of 8% in neonatal pneumonia [11], the number of babies expected to die due to pneumonia was 121. To realize this target, 1500 neonates needed to be enrolled. In view of the slow recruitment and time constraints, an interim analysis was done on the data until June 2019 (353 neonates were enrolled till then) and using the proposed predictors, the sample size was revised to 606. Nasopharyngeal swabs were also collected form 100 healthy term neonates to look at the pattern of asymptomatic viral colonisation.

The study was approved by the individual ethics committees of the participating hospitals.

Statistical analysis: Comparison of categorical variables was done by Chi square test, while continuous variables were compared using Student *t*-test. Risk ratio along with 95% CI was presented. Univariate and multivariate binary logistic regression analysis was performed to test the association between possible risk factors and outcome variables. Variables with statistical significance (*P* value <0.1) in univariate analysis were used to compute multivariate regression analysis. Adjusted odds ratio with 95% CI was calculated, taking *P* value < 0.05 as statistically significant. All statistical analysis was done on IBM SPSS version 22.

RESULTS

Out of a total of 915 eligible neonates, 500 were enrolled (**Fig. 1**). The mean (SD) birthweight of the neonates was 2635.16 (533) g with 8 (1.6%) being very low birthweight (VLBW). The mean (SD) gestational age was 37.29 (1.9) weeks, with 130 (25%) being preterm. Most of the families (52%) belonged to upper lower socioeconomic class followed by lower middle socioeconomic class (41.7%). Out of 476 neonates with known outcomes, 39 (8.2%) died. The comparison of parameters between surviving and non-surviving neonates is shown in **Table I**. There were significantly higher proportions of VLBW and preterm neonates in the non-surviving group, compared to survivors.

Onset of symptoms occurred at a mean of 5.6 days of life in the neonates who died, compared to 12.5 days in those who survived [mean difference 6.9 (95% CI 3.7, 10); *P*<0.001]. The most common presenting symptom was difficulty in feeding seen in 219 (46%)] neonates, followed by fever, noted in 110 (23%) of the neonates. The most common sign was tachypnea, mean (SD) respiratory rate being 63.7 (6.8) breaths per minute and the median Silverman Anderson score at admission was 4 (IQR 3,6). At admission, 302 (60%) neonates required oxygen, with 143 (28%) being started on CPAP, and 55 (11%) requiring intubation. The comparison of clinical features and course between surviving and non-surviving neonates is shown in **Table II**

While blood culture positivity rate was significantly higher among neonates who died, viral isolates in the nasopharynx was significantly higher among survivors,

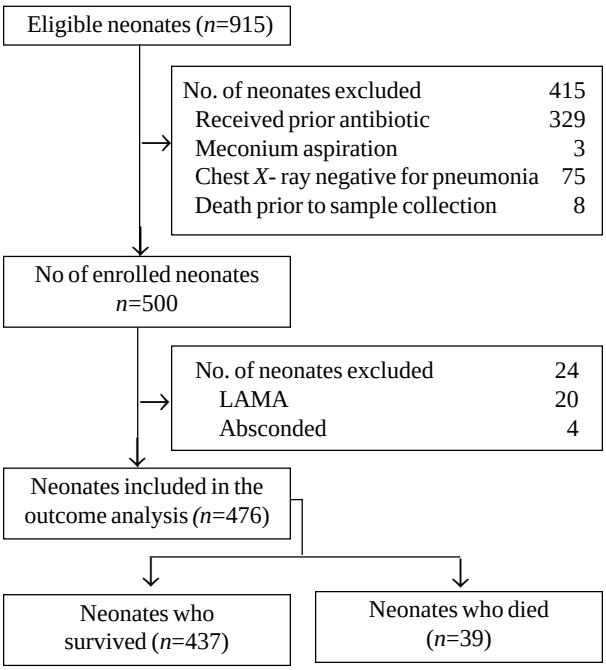

Fig. 1 Study flow chart.

Table I Comparison of Sociodemographic, Antenatal and Birth Parameters Between Surviving and Non-Surviving Neonates

Parameters	*Non-survivors (n=39)*	*Survivors (n=437)*	*Relative risk (95%CI)*
Birthweight (g)[a,e]	2403 (622)	2639 (515)	235.6 (63.4 , 407.8)[c]
Birthweight ≥1500 g[e]	3 (7.7)	5 (1.1)	6.29 (1.88, 21.07)
Gestational age (wk)[a]	36.72 (2.69)	37.29 (1.93)	0.88 (0.77, 1.01)
Preterm birth	16 (41.0)	111 (25.4)	1.91 (1.04, 3.50)
Male gender	32 (82.0)	331 (75.7)	1.42 (0.65, 3.14)
Vaginal delivery	21 (53.8)	218 (49.9)	1.14 (0.61, 2.14)
Primigravida mother	38 (97.4)	382 (87.4)	4.99 (0.69, 36.32)
Antenatal visits[b]	4 (3,4)	3 (3,4)	0.95 (0.76, 1.19)
Maternal fever[d]	1 (2.6)	11 (2.5)	1.07 (0.15, 7.79)
Apgar score (1 min)[b]	5 (5,5)	5 (5,5)	0.81 (0.54, 1.19)
Apgar score (5 min)[f]	8 (8,8)	8 (8,8)	0.65 (0.47, 0.89)
Weight at admission (g)[a,e]	2382.44 (628.47)	2691.68 (569.66)	309.12 (120.6, 497.6)[c]
Age at admission (h)[a,e]	136.46 (173.07)	301.67 (232.74)	165.2 (90.03, 240.3)[c]
Hospital stay [a,g]	5.9 (6.8)	7.81 (5.6)	1.9 (-0.02, 3.84)

Values in n (%),[a]mean (SD) or [b]median (IQR). [c]mean difference (95% CI). [d]maternal fever within 1 week prior to delivery. [e]P<0.001, [f]P=0.007, [g]P=0.05.

RSV B being the most common. (**Table III**). Overall blood culture positivity rate was 19.2%, Gram negative organisms were isolated in 45 (47%) and Gram-positive organisms in 23 (24%) neonates. Klebsiella was the commonest organism isolated and was seen in 22 neonates (23%). While 27 (28%) neonates showed fungal growth with *Candida species*,190 (38%) neonates were positive for viral PCR. Among 100 healthy term neonates, 7 were found to have asymptomatic viral colonisation (Influenza B – 5, H1N1 – 1, both influenza A and B -1)

On multivariate analysis, positive blood culture (adjusted OR 2.51, 95% CI 1.23 to 5.11; *P*=0.01) emerged as the independent predictor of mortality in neonates with pneumonia.

DISCUSSION

In this study the mortality rate due to neonatal pneumonia was found to be 8.2%. The blood culture positivity was an independent predictor of mortality, though the type of organism did not affect mortality. The mortality rate is less than that reported (12%) in the multicenter national neonatal perinatal database report [11]. In the DeNIS cohort [3] though the overall blood culture positivity among neonates with pneumonia was almost similar to our study (15% vs 19%, respectively), the mortality rate was lower (45% vs 16%, respectively) and was probably due to differences in inclusion criteria and the higher prevalence of multidrug resistant organisms. In the present study, 50% of the bacterial isolates were Gram negative, *Klebsiella* being the commonest organism reflecting community prevalence. On the other hand, two-third of the culture positive isolates were Gram negative in DeNIS study, *Acinetobacter* being the commonest isolate [3]. *Streptococcus pneumoniae*, increasingly found in possible serious bacterial infections (pSBI) among young infants, has been reported to contribute to mortality [12]. However, we did not isolate any *S. pnemoniae,* possibly due to inherent difficulty in isolating in blood cultures and the need for additional techniques. The overall microbiological yield was 53%, which is double than that reported in community-acquired serious bacterial infections [12].

The incidence of community-acquired fungal pneumonia in our cohort, confirmed by molecular diagnosis (MALDI TOF), was very high (25% of culture positive), compared to other studies [3,12], although this did not translate into higher mortality. This is intriguing as none of the neonates received any antibiotic nor were admitted in any hospital prior to enrolment.

The viral positivity rate in our study (38%) was similar to that of a community-based surveillance study (42%) involving infants with respiratory illness from Bangladesh, but neonatal pneumonia constituted only 11% in their cohort [13]. Several hospital based studies in neonates, from Asia, have reported 30% incidence of viral lower respiratory tract infections, especially due to RSV [14]. The in-hospital case fatality rate of viral pneumonia was 0.2% which is significantly lower than the reported incidence in LMIC countries [5·3% (95% CI 2·8 to 9·8)] possibly due to

Table II Comparison of Clinical Features and Course of Illness Between Surviving and Non-Surviving Neonates and Survivors

Parameters	*Non-survivors (n=39)*	*Survivors (n=437)*	*Relative risk (95%CI)*
Cough	2 (5.13)	65 (14.87)	0.34 (0.08, 1.40)
Running nose (cold)	1 (2.56)	38 (8.7)	0.29 (0.04, 2.15)
Fever	7 (17.95)	103 (23.57)	0.73 (0.32, 1.66)
Breathing difficulty	33 (84.62)	398 (91.08)	0.58 (0.25, 1.39)
Apnea[b]	5 (12.82)	14 (3.2)	3.35 (1.31, 8.57)
Cold to touch[c]	7 (17.95)	26 (5.95)	2.99 (1.32, 6.79)
Vomiting	4 (10.26)	32 (7.32)	1.43 (0.51, 4.02)
Diarrhea	0	6 (1.37)	-
Feeding difficulty	22 (56.41)	197 (45.08)	1.53 (0.81, 2.88)
Seizures[b]	8 (20.5)	33 (7.6)	2.74(1.26, 5.97)
Movement only with stimulation[b]	10 (25.64)	46 (10.53)	2.58 (1.26, 5.29)
Heart rate >180/min	4 (10.26)	46 (10.53)	0.96 (0.34, 2.71)
SAS score[a,b]	5 (4, 6)	4 (3,5)	1.278 (1.054, 1.550)
Grunting	26 (66.67)	226 (51.72)	1.77 (0.91 to 3.45)
CFT>3 seconds	5 (12.82)	48 (10.98)	1.19 (0.47, 3.04)
Temp >37.5 °C	4 (10.2)	101 (23)	0.40 (0.16, 1.03)
Temp <36.5 °C	4 (10.26)	17 (3.89)	2.48 (0.88, 6.99)
Cyanosis[c]	8 (20.51)	16 (3.66)	4.71 (2.16, 10.24)
SpO2< 90%	23 (59)	205 (46.9)	1.56 (0.84, 2.88)
Bulging anterior fontanelle	2 (5.13)	23 (5.26)	0.91 (0.22, 3.78)
Lethargy	18 (46.15)	150 (34.32)	1.56 (0.83, 2.94)
Abdominal distension[b]	6 (15.38)	22 (5.03)	2.95 (1.24, 7.05)
Hepatomegaly	4 (10.26)	51 (11.67)	1.19 (0.47, 3.04)
More than one skin pustule	1 (2.56)	1 (0.23)	6.55 (0.90, 47.73)
Respiratory support at admission			
Oxygen[d]	14 (35.9)	272 (62.24)	0.37 (0.19, 0.69)
Intubation[c]	16 (41.03)	38 (8.7)	6.28(3.06, 12.86)
CPAP	9 (23.08)	127 (29.06)	1.36(0.6, 3.14)

Values in (%) or [a]median (IQR). [b]P=0.01; [c]P<0.001; P=0.002. CPAP: continous positive airway pressure; SAS: Silverman Anderson score.

Table III Comparison of Microbiological Parameters Between Surviving and Non-Surviving Neonates

Parameters	*Non-survivors (n=39)*	*Survivors (n=437)*	*Relative risk (95%CI)*	*P value*
Blood culture positive	15 (38.4)	78 (17.8)	2.63 (1.38 - 5.01)	0.003
Gram positive	2 (5.1)	20 (4.5)	0.52 (0.12 - 2.25)	0.38
Gram negative	8(20.5)	38 (8.7)	0.49 (0.06 - 3.71)	0.49
Fungal	5(12.8)	20 (4.5)	1.46 (0.41 - 5.12)	0.56
Viral PCR positive	4 (10.3)	177 (40.5)	0.18 (0.06 - 0.525)	0.001
RSV B	3 (7.7)	118 (27)	0.24 (0.07 - 0.79)	0.01

Values in n (%). RS: respiratory syncytial virus.

better management in tertiary care centers [15]. Moreover, neonates with viral pneumonia had higher body weight and presented at a later age in the neonatal period, which could possibly explain better outcome., The most common viral isolate in the present study was RSV, consistent with the global burden, but unlike the usual pattern, type B strain was dominant, which could be another reason for better survival [14-16].

WHAT IS ALREADY KNOWN?

- Predictors of moratality in neonatal pneumonia are largely unknown.

WHAT THIS STUDY ADDS?

- Blood culture positivity independently predicts mortality in neonatal pneumonia.
- High prevalence of RSV B and *Candida* was seen in neonatal pneumonia.

The symptoms and signs used in our study were similar to those in integrated management of neonatal and childhood illness (IMNCI) and young infant study [17,18]. Though they have been shown to predict the occurrence of pBSI, our data failed to show their association with mortality.

The strength of our study was the use of a very strict case definition, which, to the best of our knowledge, is the first and largest of its kind. The limitation of the study was the inability to enroll the originally planned 1500 neo-nates, due to logistic constraints. Other etiological agents like Mycoplasma, Chlamydia, and Pneumococcus requiring special techniques for isolation, were not evaluated. The investigators involved in the inter-pretation of *X*-rays were not blinded to clinical features.

In conclusion we found blood culture positivity in neonatal pneumonia as an independent predictor of mortality. The role of fungus in community acquired neonatal pneumonia needs further exploration and there is need to be vigilant and consider early antifungal therapy especially in those who do not seem to respond. The high incidence of viral pneumonias in our study emphasizes the need to consider nasopharyngeal swab in the neonatal pneumonia work up. Vaccination against RSV immediately after birth may be a potential strategy to lower the burden of neonatal pneumonia. [19]

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Ethics clearance: (*i*) Ethics committee of Osmania medical college, Hyderabad; Reg No ECR/300/Inst/AP/2013 Date of approval June 23, 2015; (*ii*) Ethics committee of Gandhi Medical college, Hyderabad, ECR/180/Inst/AP/2013- October 13, 2015; and (*iii*) Ethics committee of Fernandez hospital, Hyderabad; ECR/933/Inst/TG/2017 – December 09, 2015.

Contributors: SK, SS, SM, JVR, MB: involved in the concep-tion, design of the project; SK,SS,SM were also involved in data analysis, drafting of manuscript; MB, SP, NPB: designed and conducted the microbiological aspects of the study; HS, AM, SL, SB, BN: involved in case enrolment and supervision. All the authors were involved in critical appraisal and have reviewed and approved the manuscript.

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