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Original Article

Risk factors of mortality in extramural neonatal sepsis: an experience from resource limited setting of central India

Rajkumar Motiram Meshram, Kalyani S. Kadu

Abstract

Background Sepsis is responsible for 30-40% of neonatal deaths which can be attributed to various maternal, neonatal, and socio-cultural risk factors. Extramural neonates have higher incidence of sepsis and sepsis related mortality due to different sources of infection, difference in levels of neonatal care, delayed referral, and treatment variation with multiple antimicrobials prior to referral.
Objective To recognize the clinical, socio-cultural, and laboratory risk factors of mortality in extramural neonatal sepsis.
Methods A prospective observational study was conducted for a year on extramural neonates with suspected sepsis. Maternal, neonatal, and sociocultural factors were analyzed.
Results Average duration of hospital stay was shorter in non-survival compared to survival neonates (P=0.01). On univariate analysis, preterm (P<0.001), weight <2500 grams (P=0.01), home delivery (P=0.004) by shaman (P=0.003), unbooked mothers(P=0.03), peripartum febrile event (P=0.02), and premature rupture of membrane >18 hours were the significant risk factors of mortality. Those neonates admitted with lethargy (P=0.04), hypothermia (P=0.01), respiratory distress (P<0.001), convulsion (P<0.0001), jaundice (P=0.006), Apgar score <5 at 1 minute (P=0.01), prolonged capillary refill time (CRT) (P<0.001), previously hospitalized (P<0.001), required mechanical ventilation (P=0.01), had thrombocytopenia (P=0.02), increased CRP (P<0.001), hypoglycemia (P=0.04), oxygen saturation ≤90% (P=0.04), abnormal cerebrospinal fluid/chest radiograph finding (P=0.002) had significantly higher mortality.
Conclusion Maternal, neonatal, and sociocultural risk factors are contributed to the development of sepsis in extramural neonates in this study. **[Paediatr Indones. 2024;64:209-17; DOI: 10.14238/pi64.3.2024.209-17**].

Keywords: *extramural neonates; outborns; risk factors of mortality; sepsis; sepsis related deaths*

Sepsis is an invasive devastating infection due to a dysregulated host response to organism.[1] Peak sepsis incidence and mortality occurs in the extreme age group due to deficient humoral and cellular immune response. Despite improvement in obstetrics, perinatal and intensive care management, neonatal sepsis is responsible for 30-40% of neonatal mortality in developing countries.[2-4] According to global estimates of neonatal sepsis, annual neonatal sepsis cases are 1.3 to 3.9 million cases with 400000-700000 annual worldwide deaths. A recent meta-analysis revealed that the incidence of neonatal sepsis is 2824 per 100000 live births with regional differences and a mortality of 17.6%.[5,6] Neonatal sepsis is classified as early onset sepsis (EOS) which is usually due to transplacental or intrapartum transmission of pathogen from mother and late onset sepsis (LOS) is due to postnatal acquisition of pathogen from community or nosocomial source with 72 hours of life as a common demarcation.[7,8]

From the Department of Pediatrics Government Medical College Nagpur, Maharashtra, India.

Corresponding author: Rajkumar Motiram Meshram. Department of Pediatrics Government Medical College Nagpur, Maharashtra, India. Phone 9822722315. Email: dr_rajmeshram@rediffmail.com.

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Neonatal sepsis has diagnostic challenges due to non-specific clinical presentation and variable laboratory results. Many of other clinical conditions mimic sepsis which leads to both over and under diagnosis and treatment. Isolation of microorganisms is the gold standard for diagnosis of neonatal sepsis but its availability is limited in constraint countries and it is positive in 50-80% at best, however negative blood culture does not rule out the disease.[1,9]

India is the first country to start nationwide programmes for mother and child health. However, in fiscal year 2020, 277 thousand neonates were born at home and a significant number of non-institutional birth or birth at limited resources needed neonatal transport.[10] Such neonates were at higher risk of sepsis as they were delivered with poor perinatal care, traveled long distances without appropriate care during transport, and had previous hospitalization and various socio-cultural practices. Prevalence of sepsis are higher in extramural neonates compared to inborn neonates (59% *vs.* 35%). The microorganisms profile and antimicrobial resistance significantly varies in extramural neonates compared to inborn neonates.[4,11,12] Around 84% deaths due to sepsis are preventable by early diagnosis and timely, appropriate clinical management.[6] In this scenario, prediction of neonatal sepsis and sepsis related mortality relies on culture-independent diagnostics and risk factors-based systems. So, this study was conducted to recognize the clinical, sociocultural, and laboratory risk factors of mortality in extramural neonates with sepsis.

Methods

A prospective observational study was carried out at a tertiary government referral hospital of central India in extramural neonates (delivered outside our hospital premises). The study was conducted over a period of one year after approval from the Institutional Ethical Committee and informed valid consent from parents. The neonates had signs and symptoms of sepsis and admitted through either outpatient or emergency department to our institute were included in the study. Neonates who died within 24 hours of hospitalization, with lethal congenital malformation, those who left the hospital against medical advice and parents of neonates not willing to participate in the study were excluded. All neonates underwent the following investigation.

1) Blood culture: with all aseptic precautions, one-ml sample of blood was collected in a blood culture bottle containing 5-10 ml of culture media before starting antibiotics. All blood culture were performed on blood agar and Macconkey's agar and was observed for 72 hours before they were reported as negative.

2) Sepsis screening: as per our hospital protocol, sepsis screen includes complete blood counts (CBC), absolute neutrophil count (ANC), and c-reactive protein (CRP). Anemia was taken as hemoglobin level <10 g/dL, leucopenia [white blood count (WBC) <5000/mm^3], leukocytosis [WBC count >20,000/mm^3], neutropenia [ANC </2000mm^3] and thrombocytopenia was defined as platelet count <100,000/mm^3. C-reactive protein was considered raised when it was elevated to above 3 mg/dL. Cerebrospinal fluid examination (CSF), urine culture, renal function test, chest and abdominal X-ray, abdominal and head ultrasound, and computed tomography of the brain were performed in indicated neonates. Abnormal chest radiograph was defined if there were unilateral or bilateral infiltrates on chest radiograph, excluding radiographic abnormalities of preterm neonates with respiratory distress syndrome. Abnormal CSF was defined if there was either abnormal cellularity or CSF culture showed growth of any microorganism. Hypoglycemia was considered when random blood sugar was < 45 mg/dL taken on a glucometer.

Suspected sepsis was defined as neonate having symptoms and/or signs of sepsis. Probable sepsis was clinical sepsis with a positive sepsis screen and proven sepsis was defined as sepsis with the growth of causative organisms in the blood culture. Early onset sepsis (EOS) was defined as clinical manifestation of sepsis appearing within 72 hours of birth, while in late onset sepsis (LOS), clinical manifestation of sepsis after 72 hours of birth. All neonates were observed for clinical events and managed according to our standard treatment protocol, and followed up to discharge or death. Those mothers who received inadequate antenatal care (<3 antenatal visit) were labelled as unbooked mothers.

Data was collected following admission, from either the mother or caregiver in a specially designed proforma for study. Maternal, neonatal, and transport

details were extracted from mother or caregiver, Apgar scores were noted from available referral documents. Socioeconomic status of parents was classified on the basis of Modified Kuppuswamy scale.

Continuous variables were presented as mean or median. Categorical variables were expressed in frequency and percentages. Continuous variables were compared between survivors and non-survivors performing independent T-test for normalized data and for non-normalized data, Mann-Whitney test was applied. Categorical variables were compared between survivors and non-survivors by performing a Chi-square test. For small numbers, Fisher exact test was used wherever applicable. Odds ratio, 95% confidence intervals were calculated to find association of different factors with mortality. Multivariate logistic regression was performed to determine independent risk factors of mortality in patients of sepsis. P value of <0.05 was considered as statistically significant. Statistical software *STATA version 14.0* was used for statistical analysis.

Results

A total of 170 extramural neonates were recruited in this study with a male female ratio of 1.39:1. Majority (64.12%) neonates were term baby with an average birth weight was 2100.28 (SD 608.04) grams. Late onset sepsis was diagnosed in 56.47% neonates and mean age at the time of admission was 75.36 (SD 32.02) hours. Majority of the neonates were delivered by vaginal route (**Table 1**). Average mileage by neonates to reach out the hospital was 67.12 (SD 38.19) km and average travel time was 2.41 (SD 1.15) hours. As the mileage and travel time was increased, the mortality was increased, indicating that mileage and travel time from birth place to the hospital were significant risk factors of mortality in extramural neonates with sepsis. Mortality was significantly higher in neonates who were transported by ambulance without a health assistant ($P<0.001$) (**Table 2**).

Lethargy, respiratory distress, and prolonged capillary refill time (CRT) were the common clinical presentations. Important laboratory finding that were recorded includes leucopenia, thrombocytopenia, oxygen saturation $\leq 90\%$, and increased CRP. Mortality was significantly higher in neonates who presented with thrombocytopenia, increased CRP, hypoglycemia, abnormal CSF, chest x-ray, and low oxygen saturation (**Table 3**). Micro-organism was isolated in 8.24% neonates. Most commonly isolated organisms were *K. pneumoniae* and *E. coli*. The mortality was significantly higher in culture proven sepsis (**Figure 1**).

Out of 170 extramural neonates with sepsis, 49 died, giving a mortality rate of 28.82%. Mortality rate in EOS was 33.78% and in LOS was 25%. The case fatality rate in clinical, probable, and culture proven sepsis was 14.61%, 38.80%, and 71.43% respectively. On univariate analysis preterm, low birth weight, home delivered by shaman, unbooked mother, peripartum febrile events, and premature rupture of membrane of >18 hours were the significant risk factors of mortality. Those neonates who were admitted with lethargy, hypothermia, respiratory distress, convulsion, jaundice, Apgar score <5 at 1 minute, prolonged CRT, previously hospitalized, and requiring mechanical ventilation had significantly higher mortality (**Table 4**). Delivery conducted by shaman, long distance, prematurity, bottle feeding, previous hospitalization, neonates presenting with lethargy, hypothermia, convulsions, prolonged CRT, and isolation of microorganisms were the independent risk factors of mortality in extramural neonates with sepsis (**Table 5**).

Discussion

Neonatal mortality is a reliable indicator for evaluating the progress of perinatal services. Sepsis is a serious bacterial infection which threatens survival during neonatal period. Various maternal, neonatal, and sociocultural factors render them susceptible for sepsis and sepsis related deaths. So, identification of such factors is important to reduce mortality.

Preterm and low birth weight neonates are more prone for sepsis and sepsis related mortality due to deficiencies in humoral and cellular immunity as they receive less maternal immunoglobulins compared to term infants, as well as preterm neonates have high tendencies for prolonged hospitalization, which increases the risk of nosocomial infection. We observed prematurity and low birth weight as the significant risk factors of mortality and our results are in concurrent

Table 1. Baseline characteristics of participants

Characteristics	All cases (N=170)	Survival (n=121)	Non-survival (n=49)	P value
Gender (male),n(%)	99 (58.24)	73 (60.33)	26 (53.06)	0.38
Gestational age, n(%)				
Preterm	58 (34.12)	30 (24.79)	28 (57.14)	<0.001
Term	109 (64.12)	89 (73.55)	20 (40.82)	
Post-term	3 (1.76)	2 (1.66)	1 (2.04)	
Weight on admission, n(%)				
<2500 g	110 (64.70)	71 (58.68)	39 (79.59)	0.01
>2500 g	60 (35.30)	50 (41.32)	10 (20.41)	
Age at admission, n(%)				
<72 h	74 (43.53)	49 (40.50)	25 (51.02)	0.20
>72 h	96 (56.47)	72 (59.50)	24 (48.98)	
Mean duration of hospital stay (SD), days	4.80 (2.85)	5.14 (3.05)	3.95 (2.08)	0.01
Mode of delivery, n(%)				
Vaginal	130 (80.59)	96 (79.34)	41 (83.67)	0.49
Caesarean	30 (17.65)	24 (19.83)	6 (12.24)	0.43
Assisted	3 (1.76)	1 (0.83)	2 (4.09)	0.20
Place of delivery, n(%)				
Primary Health Center	92 (54.12)	65 (53.72)	27 (55.10)	0.87
Rural Hospital	13 (7.65)	10 (8.26)	3 (6.11)	0.63
District Hospital	38 (22.35)	31 (25.62)	7 (14.29)	0.10
Medical College	10 (5.88)	8 (6.61)	2 (4.09)	0.72
Home	17 (10.00)	7 (5.79)	10 (20.41)	0.004
Delivery attendant, n(%)				
Traditional birth attendan	19 (11.18)	8 (6.61)	11 (22.45)	0.003
Accredited social health activist	41 (24.12)	29 (23.97)	12 (24.49)	0.82
Medical officer	83 (48.82)	62 (51.24)	21 (42.86)	0.32
Obstetrician	27 (15.88)	22 (18.18)	5 (10.20)	0.19
Residence, n(%)				
Rural	137 (80.59)	96 (79.34)	41 (83.67)	0.51
Urban	33 (19.41)	25 (20.66)	8 (16.33)	
Socioeconomic status				
Middle	41 (24.12)	27 (22.31)	14 (28.57)	0.38
Lower	129 (75.88)	94 (77.69)	35 (71.43)	
Parity, n(%)				
Primipara	71 (41.76)	53 (43.80)	18 (36.73)	0.39
Multipara	99 (58.24)	68 (56.20)	31 (63.27)	
Antenatal care, n(%)				
Booked (>3 ANC visit)	157 (92.35)	115 (95.04)	42 (85.71)	0.03
Unbooked (<3 ANC visit)	13 (7.65)	6 (4.96)	7 (14.29)	

ANC=antenatal care

with observations of other researchers.[13-15] Therefore, it is important to prevent neonates from prematurity and low birth weight by providing effective antenatal care, prompt diagnosis, and early initiation of therapy to reduce mortality.

In spite of promoting 100% institutional delivery, a significant number of births take place at home and are conducted by untrained or partially trained birth attendant in unhygienic conditions, thus neonates are more susceptible to deaths. Similar to the finding of previous studies, home delivered and delivery conducted by shaman had significantly higher mortality compared to hospital delivery or delivery conducted by trained personnel;[16-17] but some author did not reveal any significant difference in mortality with septic neonates.[15] We observed, neonates whose mothers received inadequate antenatal care had significantly higher mortality compared to neonates whose mothers received adequate antenatal care. This indicates that effective antenatal care with proper

Table 2. Transport details of participants

Transport variables	All cases (N=170)	Survival (n=121)	Non-survival (n=49)	P value
Mileage, n(%)				
Less than 20 km	7 (4.12)	6 (4.96)	1 (2.04)	<0.001
21-40 km	53 (31.18)	44 (36.35)	9 (18.37)	
41-60 km	37 (21.76)	29 (23.97)	8 (16.33)	
61-80 km	27 (15.88)	21 (17.36)	6 (12.24)	
>80 km	46 (27.06)	21 (17.36)	25 (51.02)	
Travel time, n(%)				
Less than 1h	36 (21.18)	30 (24.79)	6 (12.24)	0.004
1-2h	66 (38.82)	53 (43.80)	13 (26.53)	
2-3h	42 (24.71)	23 (19.01)	19 (38.78)	
>3h	26 (15.29)	15 (12.40)	11 (22.45)	
Mode of transport, n(%)				
Ambulance without health assistant	75 (44.12)	43 (35.54)	32 (65.31)	<0.001
Ambulance with health assistant	27 (15.88)	22 (18.18)	5 (10.2)	0.19
Private car	3 (1.76)	3 (2.48)	0	0 0.55
Auto-riksha	45 (26.48)	36 (29.75)	9 (18.37)	0.12
Motor -bike	20 (11.76)	17 (14.05)	3 (6.12)	0.19

Table 3. Clinical and laboratory risk factors of mortality in sepsis

Clinical/laboratory variables	All cases (N=170)	Survival (n=121)	Non-survival (n=49)	P value
Lethargy	126(74.12)	95(78.51)	31(63.27)	0.04
Respiratory distress	98(57.65)	85(70.25)	13(26.53)	<0.001
Apnea	20(11.76)	13(10.74)	7(14.29)	0.50
Hypothermia	71(41.76)	43(35.54)	28(57.14)	0.01
Convulsions	18(10.59)	4(3.31)	14(28.57)	<0.0001
Jaundice	80(47.06)	65(53.72)	15(30.61)	0.006
Prolonged CRT	98(57.65)	54(44.63)	44(89.80)	<0.001
Cyanosis	27(15.88)	16(13.22)	11(22.45)	0.13
APGAR score <5 at 1 minute	11(6.32)	4(3.31)	7(14.29)	0.02
Requirement of resuscitation	21(12.35)	13(10.74)	8(16.33)	0.31
Anemia (Hb <10 gm%)	35(20.59)	27(22.31)	8(16.33)	0.38
Thrombocytopenia	58(34.12)	36(29.75)	22(44.90)	0.02
Leucopenia	88(51.76)	62(51.24)	26(53.06)	0.83
ANC <500	28(16.47)	21(17.36)	7(14.29)	0.62
Increased CRP	48(28.23)	6(4.96)	42(85.71)	<0.001
Hypoglycemia	65(38.23)	38(31.40)	27(55.10)	0.004
Oxygen saturation ≤90%	87(51.18)	56(46.28)	31(63.27)	0.04
Abnormal CSF finding	13(7.64)	4(3.31)	9(18.37)	0.002
Abnormal chest radiography	46(27.06)	26(21.49)	20(40.82)	0.01
Isolation of microorganisms	14(8.24)	4(3.31)	10(20.41)	0.01

counseling and education regarding safe delivery, hygienic practices and essential newborn care is important to reduce sepsis and sepsis related mortality.

Transported neonates are prone for hypoglycemia, hypoxemia, and hypothermia. Thus anticipation, identification, and prompt intervention by health assistants is most important to reduce mortality in sick neonates. Similar to the observations of other researchers,[15,18] we observed that as the mileage and travel time increases, the mortality increases. This

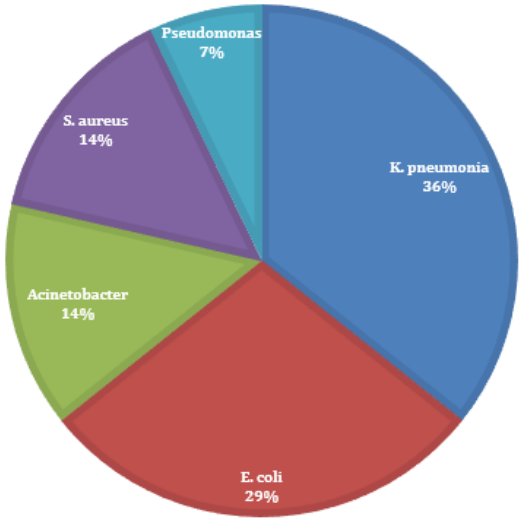

Figure 1. Distribution of isolated microorganism

Table 4. Maternal, neonatal and socio-cultural risk factors of mortality in sepsis

Variables	All cases (N=170)	Survival (n=121)	Non-survival (n=49)	P value
Maternal factors				
Peripartum febrile events	65 (38.24)	40 (33.06)	25 (51.02)	0.02
Foul smelling liquor	72 (42.35)	48 (39.67)	24 (48.98)	0.26
Premature rupture of membrane >18hs	80 (47.06)	51 (42.15)	29 (59.18)	0.04
Unclean per-vaginal examination	40 (23.53)	26 (21.49)	14 (28.57)	0.32
Prolonged labor	46 (27.06)	35 (28.93)	11 (22.45)	0.38
Neonatal factors				
Previous hospitalization	50 (29.41)	13 (10.74)	27 (55.10)	<0.001
Mechanical ventilation	12 (7.06)	5 (4.13)	7 (14.29)	0.01
Invasive procedures	63 (37.06)	43 (35.54)	20 (40.82)	0.51
Administration of parenteral fuid	45 (26.47)	32 (26.45)	13 (26.53)	0.99
APGAR score <5 at 1 minute	11 (6.32)	4 (3.31)	7 (14.29)	0.01
Requirement of resuscitation	21 (12.35)	13 (10.74)	8 (16.33)	0.31
Sociocultural factors				
Poor cord care	20 (11.76)	9 (7.44)	11 (22.45)	0.006
Poor hygienic practice at home	116 (68.24)	78 (64.46)	38 (77.55)	0.097
Bottle feeding	26 (15.29)	7 (5.79)	19 (38.78)	<0.001
Prelactal feeds	16 (9.41)	11 (9.09)	5 (10.2)	0.82

suggests that mileage and travel time are significant risk factors of mortality in extramural neonates. We also observed mortality was significantly higher in neonates who travel in an ambulance without a health assistant and no care during transport compared to those traveling in an ambulance with a health assistant [P<0.001].

Our findings are in agreement with other researchers in terms of common presentation (lethargy, respiratory distress, and jaundice).[17,19] Similar to the observation of other authors, we found neonates who presented with those symptoms and also suffered from hypothermia, convulsion, and prolonged CRT had significantly higher mortality. These may be related to the occurrence of cardiovascular collapse and metabolic derangements.[20-23]

Thrombocytopenia is a complex interaction of diffuse endothelial damage, increased platelet activation and DIC. Higher rates of leukopenia and neutropenia, refractory hypercoagulable state,

Table 5. Independent risk factors of mortality

Risk factors	Adjusted OR	95%CI	P value
Delivery conducted by traditional birth attendant	24.49	1.92 to 311.27	0.014
Travelling Distance >80 km	5.23	1.06 to 25.78	0.042
Prematurity	7.37	1.24 to 43.60	0.028
Bottle feeding	13.31	2.33 to– 75.98	0.004
Previous hospitalization	43.31	8.93 to210.20	<0.001
Lethargy	0.12	0.03 to 0.44	0.001
Hypothermia	8.91	1.73 to 45.77	0.009
Convulsions	28.87	2.77 to 300.24	0.005
Prolonged capillary refill time	22.77	2.77 to 186.70	0.004
Proven sepsis	21.97	1.83 to 263.14	0.015

thrombocytopenia, and anemia among near death newborn because of sepsis are reported by previous studies.[20,23,24] We observed thrombocytopenia as a significant risk factor of mortality while others like anemia, leukopenia, and ANC $<500/mm^3$ were not significantly associated with mortality, probably because of the small sample size of our study.

C-reactive protein is a non-specific investigation for neonatal sepsis. However, CRP has highest sensitivity, specificity and high negative and high positive predictive values. Similar to the report of other authors, we observed that increased CRP was associated with higher mortality.[14,17,18] Sepsis is usually associated with hypoglycemia due to an inhibition of gluconeogenesis, lactic acidosis and increased glucose requirements and this again was aggravated by no feeding or poor feeding during transport and absent health assistant for administering intravenous fluids. In the present study, hypoglycemia was evident in 38.23% neonates and there was significantly higher mortality in hypoglycemic neonates and our results are concomitant with the previous study[21] while other studies[14,21] found significantly higher mortality in neonates who had hyperglycemia.

In the present study, hypoxemia (oxygen saturation ≤90%) was noted in 51.18% neonates and it was one of the significant risk factors of mortality [P=0.04]. Asphyxiated neonates are more prone for sepsis due to requirement of resuscitation measure in perinatal period. We also observed abnormal CSF finding [P=0.002] and abnormal chest radiograph [P=0.01] to be significant risk factors of mortality and our findings are in agreement with the result of a previous study.[15]

Although the isolation of bacteria is the gold standard in the diagnosis of neonatal sepsis, in a large number of cases, the blood culture remained sterile despite the presence of clinical and laboratory signs, which may be attributed to small inoculums or prior antibiotic exposure. We found culture positive rate was 8.23% and the most common organism isolated was *K. pneumonie* followed by *E. coli* and 100% fatality was observed in Acinetobacter species and Pseudomonas isolates. Low rate of isolation of organisms might be due to the fact that most of the neonates had received antibiotics before referral. Similar to the observation by other authors, mortality was significantly higher with isolation of organisms.[25,26]

Poor cord care and bottle feeding were associated with poor outcome and our findings are in concomitant with various authors.[16,22,23,25,27] Therefore, it is important to educate the mother and family members regarding good hygienic practices and importance of breastfeeding to curtail the mortality. A previous study revealed that hazard of mortality among neonatal sepsis was 3 times higher if they did not initiate exclusive breastfeeding within one hour of birth as breastfeeding controls the influence on the initial exposure of newborn's intestinal mucosa to microbes and other defense factors of mother's milk including large amounts of secretory immunoglobulins A.[16]

Our study are concomitant with other researchers,[4] in terms of the occurrence of LOS that was more frequently compared to EOS. Several factors contributing to this issue such as poor hygiene practices and most of the extramural neonates were delivered at home and/or treated elsewhere.[4]

Mortality rate in this study was 28.82% which is slightly reduced compared to previous study from the similar setting (38.24%).[4] This might be because of the improvement in perinatal and transport services. Occurrence of sepsis and sepsis related deaths depends on the time of acquiring infection, the type of microorganism, the type and initiation time of antimicrobial agent. Mostly, EOS is due to acquiring infection from the maternal genital tract, before or during labor and LOS was because of sociocultural and religious factors.

As conclusion, our study revealed that risk factors contributing to the mortality of extramural neonates, includes maternal, neonatal, and socio-cultural. Therefore, these factors should be integrated in the maternal and neonatal services to reduce the mortality rate in the future.

Conflict of interest

None declared.

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