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ORIGINAL RESEARCH

# Hierarchical Predictors of Mortality in Neonatal Sepsis at Jimma Medical Center, Ethiopia: A Case–Control Study

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**Background:** Neonatal sepsis made the neonatal period the most perilous time for child survival, and it continued to cause preventable mortalities worldwide. These mortalities stem from the interaction of several factors that have not been sufficiently studied and, in some cases, remain overlooked. Thus, the study aims to investigate the predictors of mortality that arise from the interaction of these factors and quantitatively determine their etiologic fraction.

**Methods:** A case–control study with hierarchical data input was conducted at Jimma Medical Center (JMC) in Oromia, Ethiopia, spanning from May 2022 to July 2023. It employed logistic regression to calculate adjusted odds ratios (AORs) and their corresponding 95% confidence intervals (CI) at a significance level of $p \leq 0.05$. The model adjusted odds ratios (ORs) for variables within each level and farther levels and presented an etiologic fraction (EF), indicating the proportion of neonatal mortality attributable to specific factors.

**Results:** The analysis of 67 cases and 268 controls unveiled significant predictors of mortality in sepsis that emerged from distal, intermediate, and proximal levels. In the final model, thus, rural residence [AOR 3.1; 95% CI (1.5, 6.3), $p \leq 0.01$], prolonged labor [AOR 4.5; 95% CI (2.2, 9.3), $p \leq 0.01$], prematurity [AOR 3.9; 95% CI (1.9, 7.9), $P \leq 0.0$], gram-negative bacteremia [AOR 3.8; 95% CI (1.9, 7.6); $P \leq 0.01$], convulsion [AOR 3.2; 95% CI (1.6, 6.4); $P \leq 0.03$], low birth weight [AOR 2.7; 95% CI (1.3, 5.4); $P \leq 0.01$], and delayed breastfeeding [AOR 2.5; 95% CI (1.2, 4.9); $P \leq 0.01$] attributed a variable percentage of mortality.

**Conclusion:** Factors emerging and interacting at distal (residence), intermediate (prolonged labor), and proximal (prematurity, birth weight, convulsion, bacterial etiology, and feeding) levels influence neonatal mortality in sepsis at JMC. Therefore, concurrently improving rural family characteristics, managing labor duration, strengthening diagnostic stewardship, and promoting essential newborn care can actively prevent and reduce these mortalities.

**Plain Language Summary:** The existing body of literature indicates that neonatal mortality in sepsis is influenced by a complex interplay of factors at different hierarchical levels. These factors encompass maternal characteristics, neonatal health status, healthcare system capacity, and socio-economic conditions. To accurately predict outcomes related to neonatal sepsis mortality, it is vital to have a comprehensive understanding of the intricate relationship among these factors. However, previous studies have not thoroughly explored the extent and role of these factors in relation to neonatal sepsis mortality. In a recent study, researchers conducted a comprehensive investigation into the implications of factors at three levels: distal, intermediate, and proximate. Employing a case–control design and hierarchical data input, the study aimed to explore the etiological fraction associated with each level. The findings of this study shed light on the presence, interaction, and contribution of predictors at each level, emphasizing the vital importance of addressing factors at all levels to effectively prevent and control neonatal mortality in sepsis.

**Keywords:** bacteremia, factor interaction, hierarchical predictors, neonatal sepsis



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# Introduction

Neonatal sepsis, a non-monolithic systemic infection, actively serves as a pathway for severe infectious diseases, ultimately claiming the lives of thousands. It heightens the vulnerability of infants during the neonatal period, making it the most perilous time for child survival. Moreover, neonatal sepsis continues to contribute to preventable and elevated rates of neonatal mortalities worldwide.[1,2] The mortality associated with sepsis represents an invisible and marginalized trauma, tragically becoming the new normal in low- and middle-income regions. These regions face numerous challenges, including the absence of a single leading and governing entity for newborn care, insufficient financial resources allocated to neonatal care services, an inadequate number of skilled health professionals, and inadequate patient transfer mechanisms.[3,4] Likewise, limited access to quality healthcare, inappropriate diagnostic stewardship and treatment practices, heightened severity of infections, and scarcity of resources all contribute to the persistently high prevalence of neonatal sepsis in these regions.[5,6]

According to statistics, neonatal sepsis imposes a significant burden on global health, with developing regions experiencing a substantial majority (98%) of deaths, in contrast to the global average of 11% for neonatal deaths.[7] In resource-limited settings, the rates of its outcomes are influenced time, location, and interacting circumstantial factors. Collectively, these factors play a significant role, contributing to 78% of global cases and accounting for 20.3% of neonatal deaths specifically in Ethiopia and 7.1% in Jimma Medical Center.[1,2,4,8,9] The current review searched the impact of interacting factors on health and well-being using Mosley's conceptual framework,[10] and conceptualized the variables into distal, intermediate, and proximal factors. Distal variables exert an indirect influence and operate over a longer time frame, while intermediate factors function as more immediate pathways between distal and proximal factors.[10,11] Proximal factors, on the other hand, directly impact neonatal mortality and exert the most immediate and short-term effect. In predicting clinical outcomes in neonatal sepsis, proximal factors, also known as higher-level factors, reflect both distal and intermediate factors.[10,12]

Researchers in several countries, such as Turkey[13] and in developing countries, including Asia,[14] Serbia,[15] Nigeria,[16] India,[17] South Africa,[18] Tanzania,[19] the Democratic Republic of the Congo,[20] and Ethiopia,[21–25] have conducted research on predictors of neonatal mortality in neonates. These existing studies recognized significant predictors of neonatal mortality in sepsis; however, they did not sufficiently explore the hierarchical impact or the specific etiological fraction associated with these predictors. In response, the current study aims to examine the sequential chain of effects, identify hierarchical predictors, and quantify the specific attributable etiological fractions for each predictor using a conceptual framework that categorizes predictors into distal, intermediate, and proximal factors (Figure 1).

# Materials and Methods

## Study Design, Period and Setting

A case–control study was conducted at JMC, a recognized medical center in Ethiopia, from May 2022 to July 2023. The center serves a large population, with approximately 15 million outpatients and 16000 inpatients each year. The pediatric department at JMC includes a specialized neonatal intensive care unit (NICU) that admits an average of 75 neonates per month for various conditions, including sepsis. The diagnosis of neonatal sepsis in the NICU primarily relies on a clinical approach, with blood culture tests used for confirmation.

Upon admission, neonates are placed in designated rooms based on their conditions, such as critical newborn care units, septic wards, or with their mothers. The NICU is staffed by a team of six to eight nurses, three to four resident doctors, and two senior pediatricians during each shift. The pediatricians are responsible for diagnosing, admitting, and monitoring the progress and outcomes of the neonates. Other healthcare professionals in the unit handle various aspects of care, including thermoregulation, infection control, feeding, hydration, treatment, and additional support services like phototherapy, blood transfusion, laboratory tests, oxygen therapy, counseling, and pulse oximetry.[26]

## Population and Exposure

The current study involved neonates who were enrolled in an antibiotic surveillance survey conducted within the same study setting and time frame. The neonates were randomly chosen from the total population of admitted cases with suspected neonatal sepsis at the Neonatal Intensive Care Unit (NICU) of JMC. The diagnosis of sepsis in this study was

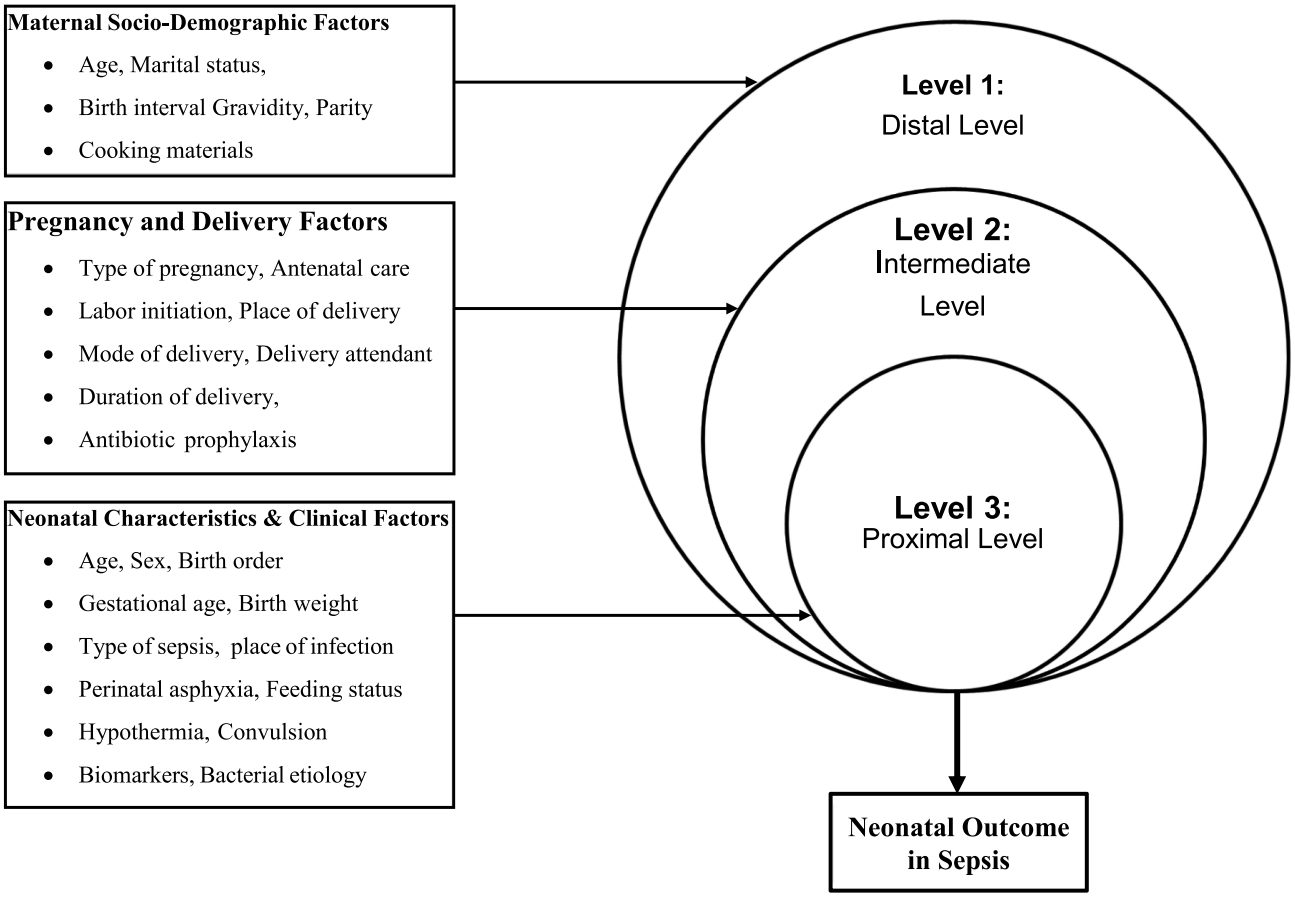


**Figure 1** Hierarchical predictors of neonatal mortality in sepsis, Ethiopia, September 2023.

determined by utilizing clinical criteria, in combination with either a biomarker or blood culture. Consequently, the study included neonates who exhibited at least one of the clinical signs typically associated with sepsis: fever (>38°C) or hypothermia (<36°C), fast breathing (>60 breaths/minute), severe chest indrawing, poor feeding, seizure, lethargy, or unconsciousness and two hematologic criteria: total leukocyte count (<5000 or >12,000 cells/$m^3$), absolute neutrophil count (<1500 cells/$mm^3$ or >7500 cells/$mm^3$), erythrocyte sedimentation rate (ESR >15/h), and platelet count (<150,000 or >440,000 cells/$mm^3$).[21] During the study, all participants were subjected to a blood culture test upon their hospital admission. The attending ward pediatrician vigilantly followed the participants within the first 6 hours of admission and maintained daily monitoring throughout their entire inpatient stay, which spanned a maximum of 28 days. During the follow-up, the pediatrician recorded the index date for participants, which was the date when the neonatal death attributed to sepsis occurred. The attending pediatrician also established case and control groups and facilitated the collection of data for both groups on exposure status to distal, intermediate, and proximal level variables (illustrated in Figure 1).

## Inclusion and Exclusion Criteria

The study employed inclusion criteria for this case–control study that involved neonates diagnosed with sepsis and admitted to the NICU under the care of a pediatrician. Moreover, these neonates had to actively participate in the follow-up study and possess baseline data to be eligible for inclusion in the recent study. On the other hand, participants were excluded from the study if they had incomplete data, if their guardians expressed disinterest or refused to provide informed consent, or if they were not closely monitored on a daily basis during their inpatient stay.

## Cases and Controls

The case subjects of the study were neonates who were admitted to the NICU with a diagnosis of neonatal sepsis and subsequently died, with the attending pediatrician confirming sepsis as the cause of death. On the other hand, the control subjects in the study were neonates who met the same criteria as the case subjects (ie, admitted to the NICU with a diagnosis of neonatal sepsis) but were confirmed to be alive by the attending pediatrician on the index date.

## Sample Size and Sampling Techniques

The sample size was calculated using STATCAL with an 8.5% estimated prevalence of the predictor variable (convulsion) among controls to detect an OR of 3.12 with a 1:4 case-to-control ratio at 80% power and a 95% CI[21,27] that ultimately yielded a total of 335 neonates (67 cases and 268 controls). The study utilized consecutive case enumeration and concurrent control selection methods to ensure the comprehensive inclusion of the calculated sample size.

## Data Source, Collection Methodology, and Quality Control

The guardians of the neonates responded to an adapted Android-based questionnaire through a face-to-face interview. The interview elicited data on sociodemographic factors, obstetrics and delivery history, neonatal characteristics, and biomarker and blood culture test results. To supplement the guardians' responses, hospital records were reviewed for these laboratory results. To enhance the accuracy of the responses, the questionnaire was translated into local languages (Afaan Oromo and Amharic) and then back-translated into English by a person unaware of the original version. Additionally, the questionnaire was pre-tested on 5% of a similar population outside the study facility. The data collection tool was validated, configured into Kobocollect, and uploaded to the Androids of four BSC health professionals who were given two days of training. The collected and uploaded data were checked for accuracy, completeness, clarity, and consistency on a regular basis by the researchers. Finally, data profiling was conducted prior to actual data analysis using frequency distributions and cross tabulations. The data was then anonymized and securely stored on the server based at the principal investigator.

## Ethics

The study received approval from the Jimma University Institute of Health Science Review Board on February 9, 2022, with reference number JUIRB32/2022. Similarly, it obtained a support letter from the Jimma Medical Center Ethical Committee on February 22, 2022, with reference number THRPGn/344/2022. Finally, the researchers obtained written informed consent from the primary guardian of each newborn prior to data collection, and hence we confirm that our study complies with the Declaration of Helsinki.

## Statistical Data Analysis

Data were exported to and analyzed in STATA version 16.0, which was initially used to analyze the descriptive distribution of characteristics among cases and controls. The bivariate analysis (P-value <0.2) and multivariate were performed separately for each level factor in binary logistic regression. Subsequently, the three levels of predictors tailored under the conceptual framework (Figure 1) were hierarchically adjusted into a multivariable logistic regression model to provide a more dynamic view of the characteristics of neonatal sepsis at each level. In the final logistic regression model, the OR was adjusted stepwise for all variables within the proximal level and the variables at lower levels at a P-value of <0.05.

The authors evaluated the impact of etiologic fraction (EF) on neonatal mortality in sepsis using formula, (Pe)*(OR-1)/OR), set for EF. Pe represented the ratio of the number of exposed cases relative to the total number of cases; the adjusted odds ratio (OR) was calculated from the logistic regression model. The authors have also calculated 95% confidence intervals for EF using the exponential function, natural logarithm, and standard error as exp(ln(adjusted OR) ± 1.96 * SE).[28] Each regression model was subjected to an ROC curve analysis for predictive capacity and a Hosmer–Lemeshow goodness-of-fit test for goodness-of-fit test. For all models, the area under the curve was greater than 0.5, showing a high predictive value, while the pseudo-$R^2$ values confirmed the model's goodness of fit with results of 0.0797, 0.1634, and 0.3452 for models 1, 2, and 3, respectively.

# Results

## Description of Characteristics Among Cases and Controls

In a case–control study that recruited 335 mother-neonate pairs (67 cases and 268 controls), the data were nested in distal, intermediate, and proximate levels, with one block in each level. The findings at the distal level revealed that the majority of participants (50.7%) were from rural settings, and a higher proportion of cases (71.6%) were from rural areas compared to controls (45.5%). Furthermore, a larger percentage of cases (20.9%) were from mothers aged 35 years and older compared to controls (6.0%). Similarly, a higher proportion of cases (79.1%) occurred in households primarily using wood for cooking family food, while controls had a lower proportion (69.0%). The characteristics of the participants, such as marital status, gravidity, parity, and interval between deliveries, were comparable between cases and controls at the distal level, with differences ranging from 0.1% to 8.8% for all specified variables (Table 1).

**Table 1** Distal Level Characteristics of Cases (n = 67) and Controls (n = 268) at JMC, Ethiopia

| Distal Level Factors | Cases: n (%) | Control: n (%) | Total: n (%) |
|---|---|---|---|
| **Residence type** | | | |
| Rural | 48(71.6) | 122(45.5) | 170(50.7) |
| Urban | 19(28.4) | 146(54.5) | 165(49.3) |
| **Maternal age** | | | |
| ≤19 year | 11(16.4) | 43(16.0) | 54(16.1) |
| 20–34 year | 42(62.7) | 209(78.0) | 251(74.9) |
| ≥35 year | 14(20.9) | 16(6.0) | 30(9.0) |
| **Marital status of the mother** | | | |
| Married | 66(98.5) | 265(98.9) | 331(98.8) |
| Others** | 1(1.5) | 3(1.1) | 4(1.2) |
| **Number of pregnancies (including the index neonate) the mother experienced** | | | |
| Primigravid | 21(31.3) | 107(39.9) | 128(38.2) |
| 2–4 | 32(47.8) | 120(44.8) | 152(45.4) |
| ≥5 | 14(20.9) | 41(15.3) | 55(16.4) |
| **Number of deliveries (including the index neonate) the mother experienced** | | | |
| Primiparous | 21(31.3) | 107(39.9) | 128(38.2) |
| Multiparous | 46(68.7) | 161(60.1) | 207(61.8) |
| **Delivery interval with the previous sibling** | | | |
| First child | 21(31.3) | 107(39.9) | 128(38.2) |
| <2 year | 13(19.4) | 37(13.8) | 50(14.9) |
| ≥2 years | 33(49.3) | 124(46.3) | 157(46.9) |
| **Materials the household mainly used to cook family foods** | | | |
| Wood | 53(79.1) | 185(69.0) | 238(71.0) |
| Animal waste | 4(6.0) | 9(3.4) | 13(3.9) |
| Electric power | 10(14.9) | 74(27.6) | 84(25.1) |

**Note**: Others **(3 cohabited and 1 single).

At the intermediate level, cases exhibited higher percentages of multiple pregnancies (17.9% vs 9.3%), home deliveries (16.4% vs 9.7%), labors lasting more than 24 hours (55.2% vs 24.3%), cesarean deliveries (34.3% vs 23.1%), and not receiving antibiotic prophylaxis during labor (65.7% vs 56.7%). Whereas, the proportions of cases and controls were comparable for maternal antenatal care visits (98.9% vs 98.5%), induced labor (9.0% vs 7.5%), and spontaneous labor initiation (73.1% vs 69.4%) (Table 2).

At the proximal level, there were higher percentages of neonates aged less than 3 days at admission (cases: 59.7% vs controls: 57.1%), female sex (cases: 44.8% vs controls: 38.8%), higher birth order (cases: 31.3% vs controls: 20.9%), lower gestational age (cases: 61.2% vs controls: 25.4%), birth weight below 2500g (cases: 50.7% vs controls: 21.6%), early onset of sepsis (cases: 67.2% vs controls: 64.9%), and not being breastfed within an hour after birth (cases: 59.7% vs controls: 31.0%) among cases compared to the controls. Furthermore, cases had a higher proportion of suspected hospital-based infection (cases: 56.7% vs controls: 42.5%), hypothermia (cases: 41.8% vs controls: 25.7%), convulsions (cases: 67.2% vs controls: 36.9%), leukopenia (cases: 13.4% vs controls: 5.2%), and gram-negative bacteremia (cases: 55.2% vs controls: 22.8%) compared to the control groups. Except for birth asphyxia and feeding patterns, which showed similar rates between cases and controls, controls had a higher number than cases in all other categories (Table 3).

## Predictors and Attributes of Neonatal Sepsis Mortality

### Single Level and Single Block Predictors

Table 4 presents the significant results of bivariate and multivariate analyses, which examined variables at three different levels within a single block. The multivariate analysis revealed independent predictors of neonatal mortality in sepsis at

**Table 2** Intermediate Level Characteristics of Cases (n = 67) and Controls (n = 268) at JMC, Ethiopia

| **Intrapartum Antibiotic Prophylaxis** | | **Cases** | **Controls** | **Total** |
|---|---|---|---|---|
| | | **n (%)** | **n(%)** | **n(%)** |
| Type of pregnancy | Multiple | 12(17.9) | 25(9.3) | 37(11.0) |
| | Singleton | 55(82.1) | 243(90.7) | 298(89.0) |
| ANC contacts (>3) | Yes | 66(98.5) | 265(98.9) | 331(98.8) |
| | No | 1(1.5) | 3(1.1) | 4(1.2) |
| Place of delivery | Home | 11(16.4) | 26(9.7) | 37(11.0) |
| | Health facility | 56(83.6) | 242(90.3) | 298(89.0) |
| Labor initiation | Induced | 6(9.0) | 20(7.5) | 26(7.8) |
| | Elective cesarean section | 12(17.9) | 62(23.1) | 74(22.1) |
| | Spontaneously | 49(73.1) | 186(69.4) | 235(70.1) |
| Delivery attendant | Relative | 10(14.9) | 24(9.0) | 34(10.1) |
| | Non-obstetrician health professions | 28(41.8) | 137(51.1) | 165(49.3) |
| | An obstetrician | 29(43.3) | 107(39.9) | 136(40.6) |
| Duration of labor | Above 24 hours | 37(55.2) | 65(24.3) | 102(30.4) |
| | ≤ 24 hours | 30(44.8) | 203 (69.5) | 233(69.6) |
| Mode of delivery | Cesarean- section | 23(34.3) | 62(23.1) | 85(25.4) |
| | Non-cesarean | 44(65.7) | 206(76.9) | 250(74.6) |
| Intrapartum antibiotic prophylaxis | Yes | 23(34.3) | 116(43.3) | 139(41.5) |
| | No | 44(65.7) | 152(56.7) | 196(58.5) |

**Table 3** Neonatal (Proximal) Characteristics of Cases (n = 67) and Controls (n = 268) at JMC, Ethiopia

| Proximal Level Factors | | Cases: n (%) | Controls: n (%) | Total: n (%) |
|---|---|---|---|---|
| Age at admission(days) | ≤3 | 40(59.7) | 153(57.1) | 193(57.6) |
| | >3 | 27(40.3) | 115(42.9) | 142(42.4) |
| Sex | Male | 37(55.2) | 164(61.2) | 201(60.0) |
| | Female | 30(44.8) | 104(38.8) | 134(40.0) |
| Birth order | First | 21(31.3) | 109(40.7) | 130(38.8) |
| | 2–3 | 25(37.3) | 103(38.2) | 128(38.2) |
| | ≥4 | 21(31.3) | 56(20.9) | 77(23.0) |
| Gestational age at birth | <37 weeks | 41(61.2) | 68(25.4) | 109(32.5) |
| | ≥37 weeks | 26(38.8) | 200(74.6) | 226(67.5) |
| Birth weight | <2500g | 34(50.7) | 58(21.6) | 92(27.5) |
| | ≥2500g | 33(49.3) | 210(78.4) | 243(72.5) |
| Breast feeding practice (fed within an hour at birth) | No | 40(59.7) | 83(31.0) | 123(36.7) |
| | Yes | 27(40.3) | 185(69.0) | 212(63.3) |
| Type of sepsis | Early onset | 45(67.2) | 174(64.9) | 219(65.4) |
| | Late onset | 22(32.8) | 94(35.1) | 116(34.6) |
| Possible place of infection | Hospital | 38(56.7) | 114(42.5) | 152(45.4) |
| | Community | 29(43.3) | 154(57.5) | 183(54.6) |
| Peri-natal asphyxia | Yes | 12(17.9) | 49(18.3) | 61(18.2) |
| | No | 55(82.1) | 219(81.7) | 274(81.8) |
| Poor feeding at admission | Yes | 11(16.4) | 54(20.1) | 65(19.4) |
| | No | 56(83.6) | 214(79.9) | 270(80.6) |
| Hypothermia | Yes | 28(41.8) | 69(25.7) | 97(29.0) |
| | No | 39(58.2) | 199(74.3) | 238(71.0) |
| Convulsion at admission | Yes | 45(67.2) | 99(36.9) | 144(43.0) |
| | No | 22(32.8) | 169(63.1) | 191(57.0) |
| Total leukocytes counts | Leukopenia | 9(13.4) | 14(5.2) | 23(6.9) |
| | Normal range | 49(73.1) | 212(79.1) | 261(77.9) |
| | Leukocytosis | 9(13.4) | 42(15.7) | 51(15.2) |
| Blood culture test result | Gram- Bacteria | 37(55.2) | 61(22.8) | 98(29.3) |
| | $Gram^{+}$ bacteria | 3(4.5) | 33(12.3) | 36(10.7) |
| | No bacteria | 27(40.3) | 174(64.9) | 201(60.0) |

each level. At the distal level, rural residence (AOR = 3.1; 95% CI: 1.7, 5.5; $p < 0.01$) and maternal age of 35 and older (AOR = 4.2; 95% CI: 1.9, 9.4; $p < 0.01$) were identified as significant predictors. At the intermediate level, multiple pregnancies (AOR = 3.1; 95% CI: 1.4, 7.1), labor exceeding 24 hours (AOR = 3.8; 95% CI: 2.1, 6.7; $p < 0.01$), cesarean

**Table 4** Bivariate and Multivariate Analyses of Variables at Three Levels Within a Single Block

| Variables | Categories | Cases (n) | Control (n) | Bivariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|---|---|---|
| | | | | P-value | UOR (95% CI) | P-value | AOR (95% CI) |
| **Distal level Factors** | | | | | | | |
| Residence type | Rural | 48 | 122 | 0.01 | 3.0(1.7,5.4) | 0.01 | 3.1(1.7,5.5) |
| | Urban | 19 | 146 | 1 | 1 | | 1 |
| Maternal age | ≤19 year | 11 | 43 | 0.53 | 0.8(0.4.1.7) | 0.64 | 1.2(0.1,2.6) |
| | 20–34 year | 42 | 209 | | 1 | | 1 |
| | ≥35 year | 14 | 16 | 0.01 | 3.4(1.3,9.1) | 0.01 | 4.2(1.9,9.4) |
| **Intermediate level** | | | | | | | |
| Type of pregnancy | Multiple | 12 | 25 | 0.05 | 2.1(1.0,4.5) | 0.01 | 3.1(1.4,7.1) |
| | Singleton | 55 | 243 | | 1 | | 1 |
| Duration of labor | Above 24 hours | 37 | 65 | 0.01 | 3.8(2.2,6.7) | 0.01 | 3.8(2.1,6.7) |
| | ≤ 24 hours | 30 | 203 | | 1 | | 1 |
| Mode of delivery | Cesarean- section | 23 | 62 | 0.06 | 1.8(1.0,3.2) | 0.01 | 2.6(1.3,5.5) |
| | Non-cesarean | 44 | 206 | | 1.0 | | 1 |
| Intrapartum antibiotic prophylaxis | No | 44 | 152 | 0.10 | 1.4(0.8,2.5) | 0.01 | 2.7(1.3,5.6) |
| | Yes | 23 | 116 | | 1 | | 1.0 |
| **Proximal level** | | | | | | | |
| Gestational age at birth | <37 weeks | 41 | 68 | 0.01 | 4.6(2.6,9.1) | 0.01 | 3.3(1.7,6.2) |
| | ≥37 weeks | 26 | 200 | | 1 | | 1.0 |
| Birth weight | <2500g | 34 | 58 | 0.01 | 3.8(2.2,6.7) | 0.01 | 2.7(1.4,5.2) |
| | ≥2500g | 33 | 210 | | 1 | | 1.0 |
| Breast feeding practice (fed within an hour at birth) | No | 40 | 83 | 0.01 | 3.3(1.9,0.7) | 0.01 | 2.6(1.4,0.9) |
| | Yes | 27 | 185 | | 1 | | 1.0 |
| Convulsion at admission | Yes | 45 | 99 | 0.02 | 3.5(2.0,6.1) | 0.01 | 3.5(1.8,6.7) |
| | No | 22 | 169 | | 1 | | 1.0 |
| Blood culture test result | Gram- Bacteria | 37 | 61 | 0.01 | 3.9(2.2,6.9) | 0.01 | 3.9(2.0,7.4) |
| | $Gram^{+}$bacteria | 3 | 33 | 0.4 | 0.6(0.2,2.0) | 0.5 | 0.6(0.2,2.4) |
| | No bacteria | 27 | 174 | | 1 | | 1.0 |

deliveries (AOR = 2.6; 95% CI: 1.3, 5.5; $p < 0.01$), and lack of intrapartum antibiotic prophylaxis (AOR = 2.7; 95% CI: 1.3, 5.6; $p < 0.01$) were identified as significant predictors. Similarly, at the proximal level, gestational ages below 37 weeks/prematurity (AOR = 3.3; 95% CI: 1.7, 6.2; $p < 0.01$), birth weight below 2500g (AOR = 2.7; 95% CI: 1.4, 5.2; $p < 0.01$), delayed breastfeeding initiation at birth (AOR = 2.6; 95% CI: 1.4, 9.0; $p < 0.01$), convulsions (AOR = 3.5; 95% CI: 1.8, 6.7; $p < 0.02$), and confirmed gram-negative bacteremia (AOR = 3.9; 95% CI: 2.0, 7.4; $p < 0.01$) were identified as significant predictors of neonatal mortality resulting from sepsis.

## Hierarchical Predictors of Neonatal Mortality from Sepsis

In the hierarchical analysis, several factors were determined to be significant predictors of neonatal mortality in sepsis at the intermediate level. These included rural residence [AOR 3.2; 95% CI (1.7, 5.9; p ≤ 0.01)], maternal age of 35 and older [AOR 5.0; 95% CI (2.1, 12.1); p ≤ 0.01], multiple pregnancies [AOR 2.9; 95% CI (1.6, 6.6); p ≤ 0.01], and prolonged labor [AOR 4.5; 95% CI (2.4, 7.9); p ≤ 0.01]. Further adjustment of these lower factors with proximal-level factors revealed seven final significant predictors, including prolonged labor [AOR 4.5; 95% CI (2.2, 9.3); p ≤ 0.01], gestational age less than 37 weeks [AOR 3.9; 95% CI (1.9, 7.9); p ≤ 0.01], confirmed gram-negative bacteremia [AOR 3.8; 95% CI (1.9, 7.6); p ≤ 0.01], convulsion [AOR 3.2; 95% CI (1.6, 6.4); p ≤ 0.03], living in a rural setting [AOR 3.1; 95% CI (1.5, 6.3); p ≤ 0.01], birth weight less than 2500g [AOR 2.7; 95% CI (1.3, 5.4); p ≤ 0.01], and not receiving breastfeeding within an hour of birth [AOR 2.5; 95% CI (1.2, 4.9); p ≤ 0.01] (Figure 2).

Elaboratively, the results of the hierarchical analysis indicated that neonates living in rural settings had a significantly heightened risk of mortality [AOR 3.2; 95% CI (1.5, 6.3), p ≤ 0.01] from neonatal sepsis compared to their urban counterparts. It also showed that neonates who encountered a prolonged labor above 24 hours have 4.5 times [AOR 4.5; 95% CI (2.2, 9.3), p ≤ 0.01] risk of mortality from sepsis when compared to a neonate with shorter period of labor. Similarly, neonates with a gestational age of less than 37 weeks face 3.9 times higher risk of mortality [AOR 3.9; 95% CI (1.9, 7.9), P ≤ 0.0] from neonatal sepsis when compared to neonates with a gestational age of 37 weeks or more at birth. Neonates with sepsis detected for gram-negative bacteremia have a mortality risk around four times [AOR 3.8; 95% CI (1.9, 7.6); P ≤ 0.01] higher than those of no growth in blood culture. Likewise, neonates with sepsis who experienced convulsions during their hospital stay have had 3.8 times higher risk of mortality [AOR 3.2; 95% CI (1.6, 6.4); P ≤ 0.03] from neonatal sepsis compared to neonates who did not experience convulsions. It also revealed that neonates with sepsis who has a birth weight below 3200 grams are 2.7 times more likely to die from neonatal sepsis [AOR 2.7; 95% CI (1.3, 5.4); P ≤ 0.01] when compared to neonates who weigh 3200 grams or more at birth. Finally, it was indicated that non-breastfed neonates of sepsis cases have more than 2.5 times higher mortality odds [AOR 2.5; 95% CI (1.2, 4.9); P ≤ 0.01] than those breastfed within the first hour after birth (Figure 2).

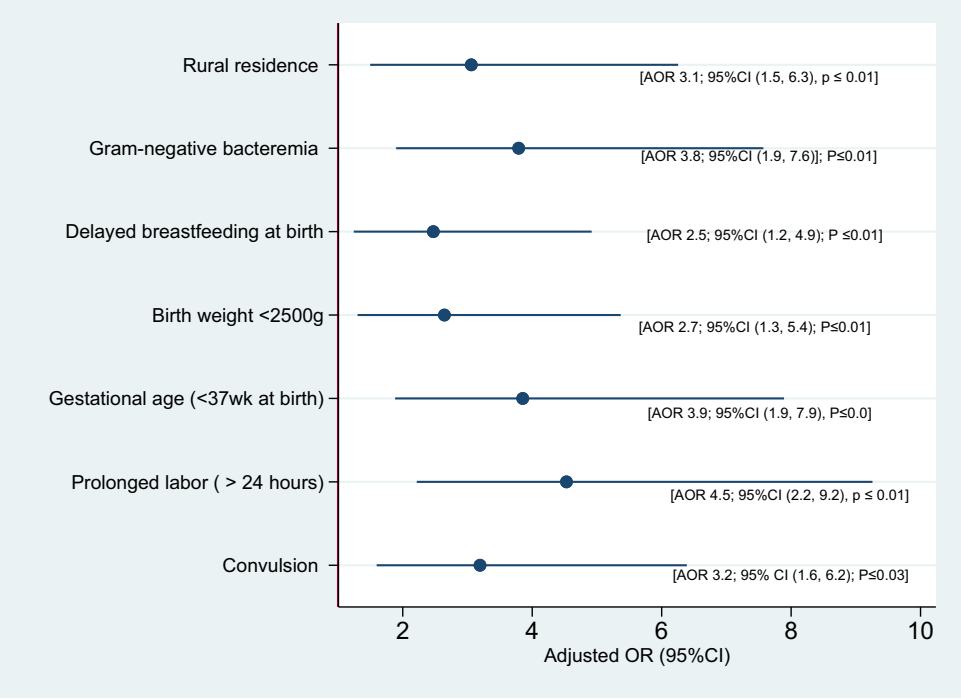


**Figure 2** Hierarchical predictor of mortality in neonatal sepsis at JMC, Ethiopia.

**Table 5** AOR and EF Proportion Derived from Hierarchical Multivariable Logistic Regressions on the Predictors of Neonatal Mortality from Sepsis at JMC, Ethiopia

| Predictors | Cases(n) | Controls (n) | Proportion of Died Case (p=n/N) | Model 3 AOD | Model 3: EF %(95% CI) |
|---|---|---|---|---|---|
| **Distal level -Residence setting** | | | | | |
| Rural | 48 | 122 | 0.14 | 3.1 | 9.5(8.5,10.4) |
| Urban | 19 | 146 | 0.06 | 1.0 | |
| **Intermediate Level-Duration of labor in hours** | | | | | |
| ≥24 | 37 | 65 | 0.11 | 4.5 | 8.6(8.4,8.8) |
| <24 | 30 | 203 | 0.09 | 1.0 | |
| Proximal Level 33.7 | | | | | |
| **Gestation age at birth (in complete weeks)** | | | | | |
| <37 | 41 | 68 | 0.12 | 3.9 | 8.9(8.4,9.4) |
| ≥37 | 26 | 200 | 0.08 | 1.0 | |
| **Blood culture test results** | | | | | |
| Gram negative | 37 | 61 | 0.11 | 3.8 | 8.1(7.8, 8.5) |
| Gram positive | 3 | 33 | 0.01 | 0.6 | |
| No bacteria | 27 | 174 | 0.08 | 1.0 | |
| **History of convulsion at admission** | | | | | |
| Yes | 45 | 99 | 0.13 | 3.2 | 8.9(8.6,9.3) |
| No | 22 | 169 | 0.07 | 1.0 | |
| **The weight of the neonate at birth (in grams)** | | | | | |
| <2500 | 34 | 58 | 0.1 | 2.7 | 6.3(5.9,6.6) |
| ≥2500 | 33 | 210 | 0.1 | 1.0 | |
| **Breast feeding practice (fed within an hour at birth)** | | | | | |
| No | 40 | 83 | 0.12 | 2.5 | 7.2(6.8,7.6) |
| Yes | 27 | 185 | 0.08 | 1.0 | |

### Proportion of Hierarchical Neonatal Mortality Predictors

The EF analysis results showed that various factors contributed to neonatal mortality from sepsis. Rural residence accounted for 9.5% (95% CI: 8.5, 10.4) of the mortality rate, while prolonged labor contributed 8.6% (95% CI: 8.4, 8.8). Prematurity contributed 8.9% (95% CI: 8.4, 9.4), and gram-negative bacteremia accounted for 8.1% (95% CI: 7.8, 8.5) of sepsis-related neonatal mortality. Likewise, convulsion, birth weight below 2500 g, and not initiating breastfeeding within the first hour of delivery represented 8.9% (95% CI: 8.6, 9.3), 6.3% (95% CI: 5.9, 6.6), and 7.2% (95% CI: 6.8, 7.6) of the mortality, respectively (Table 5).

## Discussion

In this research, a case–control design and hierarchical data entry were utilized to examine the factors influencing neonatal mortality in sepsis. The primary objective was to obtain a comprehensive understanding of predictors by

considering different levels within the hierarchy.[28] Moreover, etiologic fraction analysis was executed to assess the contribution of each predictor. Based on the current study result, the occurrence of neonatal mortality from sepsis was related to manifold factors such as rural residence (distal level factor), prolonged labor (intermediate level factor) and proximal level factors. Curiously, these factors demonstrated varying degrees of impact on mortality at different levels of the hierarchy, with certain factors exerting a stronger influence than others. For example, the analysis provided that when incorporating distal factors into intermediate factors, the ability to predict neonatal mortality from sepsis was diminished for the mode of delivery and antibiotic prophylaxis. Similarly, when integrating lower-level factors into proximal factors, maternal age and type of pregnancy lost their predictive power. However, the predictive power of gestational age increased when adjusted with lower-level factors, while the predictive power of gram-negative bacteremia, breastfeeding practices, and birth weight remained relatively stable. The study also highlighted that the influence of place of residence and duration of labor sequentially mediated the prediction of neonatal mortality from sepsis within and beyond their respective levels.

According to the study, rural residence setting escalates neonatal mortality across distal, intermediate, and proximal levels. This implies that living in rural settings has a detrimental impact on the mortality of neonates from sepsis, through working with other factors. It revealed that at the proximal level, rural residence contributes to a 9.5% of preventable neonatal mortality within the population under study, and it increasingly pronounced when adjusted to the proximal level factors, illustrating a stronger connection between rural residence and mortality resulting from neonatal sepsis. The association between rural residence and neonatal mortality observed in this study is consistent with findings reported in various locations,[29] and these results appear to be reasonable and justifiable. Global reports indicate that neonates living in rural settings often delay seeking healthcare until their condition worsens, or they are referred due to complications related to sepsis.[30] Additionally, families of rural neonates receiving care at tertiary hospitals tend to provide lesser assistance to healthcare professionals due to factors such as healthcare expenses, difficulties in adapting to the healthcare environment, and unfavorable pregnancy and delivery histories (such as multiple pregnancies, higher birth order, or poor nutritional status). Literature also suggests that rural families may face challenges in establishing a strong partnership with clinicians, limited participation in bedside rounds, and ineffective communication with intensivists, which can further exacerbate these conditions compared to urban families.[31]

Likewise, prolonged labor was identified as a factor that sequentially influences the mortality of neonates from sepsis. This influence occurs at both the intermediate and proximate levels, indicating that the duration of labor can have both a direct effect and a mediating effect on neonatal mortality from sepsis. The result is characteristically similar to the study results reported from Brazil, Taiwan, and northwest Ethiopia.[25] Illustratively, the factor attributed 8.6% of mortality at proximate level, and reasonably, the initial role could be related to complications during delivery and the predisposition of the neonate to other worsening conditions. Furthermore, during prolonged labor, neonates require increased attention from healthcare providers. However, due to the priority given to the well-being of the mother, the care provided to the neonates is often compromised. This compromised care has adverse effects on the condition of the newborns, particularly in situations where there are limited resources and a lack of neonatal golden hour initiatives in the healthcare facility. Moreover, in a prolonged labor, the neonates require increased attention from the care provider but usually compromised because of maternal priority. It, then, adversely impacts the condition of the neonates, especially in situations where there are limited resources,[4] the absence of neonatal golden hour initiatives in the facility[32] and the lack of a single leading and governing entity for newborn care.[4]

In addition to the lower-level factors mentioned earlier, the study revealed a potentiating link between low gestational age and neonatal mortality from sepsis. This result shares similarities with previous study reports in Asia,[14] Serbia,[15] Nigeria[16] and northwest[25] and southern Ethiopia.[21] Premature neonates, born before full term, have a higher risk of sepsis mortality, with the likelihood being three times higher. The EF for low gestational age estimates 8.9% of avoidable neonatal mortality from sepsis. Premature infants often have immature immune responses, making them more vulnerable to infections and less capable of effectively fighting off pathogens.[33] Additionally, their underdeveloped organs and limited physiological reserves further increase the risk of complications and reasonably worsen in the presence of lower level independent factors such rural residence.[34]

A recent study confirmed a strong association between gram-negative bacteremia and neonatal mortality. Gram-negative bacteremia accounted for approximately 8.1% of preventable neonatal mortalities, emphasizing the significance of implementing effective management strategies to prevent these fatalities.[35] This association is supported by several studies conducted in Serbia,[15] South Africa,[18] Democratic Republic of the Congo,[20] Tanzania[19] and Nigeria,[16] which consistently

demonstrate an increased neonatal mortality risk associated with gram-negative bacteremia. It is reasonable that Gram-negative bacteria have a concerning tendency to colonize medical devices, increasing the likelihood of healthcare-associated infections that pose a significant risk of mortality in neonates.[5] These bacteria are known for their heightened pathogenicity, virulence, antibiotic resistance, severity of illness, and the potential for delayed diagnosis,[5] all of which contribute to the challenges faced in their treatment. The emergence of multidrug-resistant strains within this bacterial group, particularly that producing extended-spectrum beta-lactamase (ESBL), further complicates the management of neonatal infections, leading to an increased risk of mortality.[5] Additionally, gram-negative bacteria elicit a strong immune response, lipopolysaccharide effect, causing inflammation that can progress to septic shock and organ failure, ultimately resulting in neonatal mortality.[36]

Besides gram-negative bacteremia, prematurity and low birth weights are also recognized as predictors of neonatal mortality from sepsis. Low-birth-weight infants are more than two-and-a-half times more likely to die from sepsis compared to normal-weight neonates and contribute to 6.3% of avoidable mortality. This finding coincides with previous studies of Asia,[14] Peru,[37] Serbia,[15] Nigeria,[16] and India[17] and northwest Ethiopia,[25] and indicates that interventions to address the specific challenges faced by low-birth-weight neonates could potentially avoid approximately 6.3% of neonatal mortality from sepsis. Studies have implicated this finding in several countries, including Ethiopia. The weaker immune systems, reduced fat stores, limited protective barriers as well as the lack of neonatal golden hour protocol and early initiation of breastfeeding make these infants more vulnerable to sepsis and its adverse effects.[32,38]

The study findings indeed identified convulsions as a significant predictor of an elevated risk of mortality, with an adjusted odds ratio of 3.2. This indicates that individuals experiencing convulsions are more likely to face a higher mortality rate compared to those without convulsions. Furthermore, the study estimated that approximately 8.9% of neonatal deaths can be attributed to convulsions, highlighting the substantial role of the prevention of convulsions on overall mortality within the neonatal population. Former studies in different areas like Ethiopia[21] agree with the current result and put forward a possible explanation that mainly indicates the advancement of sepsis and underlying central nervous system involvement, hypoxic-ischemic injury, excitotoxicity, disruption of the blood–brain barrier (BBB), and oxidative stress.[34,39] These conditions usually occur with severe sepsis, which is characterized by a systemic response to infection and affects various organs, including the brain. The infection can spread throughout the body, potentially compromising the blood–brain barrier and leading to neuroinflammation and brain damage.[39] This inflammation, triggered by the infection and pro-inflammatory molecules, can then damage neurons and other brain cells. It also worsens the situation by causing abnormal electrical activity in the brain, leading to excitotoxicity, an excessive influx of calcium ions into neurons, disrupting normal cellular processes, and potentially leading to cell death.[34]

Finally, the researchers observed that not initiating breastfeeding within this timeframe was a significant predictor of mortality, with an adjusted odds ratio of 2.5. This means that the odds of mortality were nearly three times higher for infants who did not begin breastfeeding within the first hour compared to those who did. Furthermore, the study identified that the predictor contributes 7.2% (EF) of neonatal mortality from sepsis. In other words, approximately 7.2% of neonatal mortality cases caused by sepsis could be attributed to delayed initiation of breastfeeding. This finding is commensurate with several previous studies conducted in Peru,[37] northwest Ethiopia,[25] and public hospitals in Southern Ethiopia[40] and suggests that promoting early breastfeeding initiation could potentially reduce the incidence of neonatal mortality from sepsis by addressing this particular risk factor. Researchers have delved into several reasons why breastfeeding can have these positive effects, including the presence of antibodies, immune factors, enhanced gut integrity, and nutritional balance.[38] Breast milk is essential for infants due to its high concentration of antibodies like IgA, immune cells, growth factors, prebiotics, and probiotics, with the initial breast milk, known as colostrum, being particularly rich in these immune factors. These antibodies provide passive immunity, protecting neonates until their immune system fully develops. Breast milk also promotes a healthy gut lining, preventing harmful pathogens from invading or preventing bacterial translocation into the bloodstream and reducing the risk of conditions like necrotizing enterocolitis.[34] The balanced nutrition of this food, which includes carbohydrates, proteins, fats, vitamins, and minerals, promotes healthy growth and reduces the risk of mortality in neonates with sepsis.[38]

Generally, the hierarchical analysis revealed that lower-level variables, such as distal and intermediate factors, significantly influence the prediction of higher-level variables, enhancing the understanding of sequential interaction and impact on neonatal sepsis treatment outcomes. This approach provided a more nuanced understanding of the

relationships between different factors and their collective contribution to neonatal mortality, highlighting the crucial role of lower-level variables in predicting neonatal sepsis mortality. However, it is important to acknowledge that the study focused exclusively on a specific subset of individuals who had access to or utilized healthcare services provided by the facilities. Therefore, it is important to exercise caution when using the results due to the potential variations in characteristics or experiences between individuals who visited the facility and those who did not.

## Conclusions and Recommendations

Generally, the study investigated the predictors of neonatal mortality caused by sepsis using a hierarchical analysis. It was found that lower-level variables, including distal and intermediate factors, significantly influenced higher-level variables and contributed to avoidable neonatal mortality caused by sepsis. Specifically, neonates residing in rural settings faced a higher risk of mortality, with distal factors playing a prominent role in this outcome. Prolonged labor lasting more than 24 hours also contributed to increased mortality. Additional predictors of mortality included prematurity, confirmed gram-negative bacteremia, convulsion, low birth weight, and delayed breastfeeding. The study recommends improving healthcare access in rural settings, monitoring prolonged labor, promoting immediate breastfeeding, addressing low birth weight and preterm births, implementing strategies for preventing and managing gram-negative bacteremia, and promptly recognizing and managing neonatal convulsions to reduce the collective effect of the predictors.

## Abbreviations

AOR, Adjusted Odds ratio; CI, Confidence interval; EF, etiologic fraction; JMC, Jimma Medical Center.

## Data Sharing Statement

Data are available at Jimma University, and researchers who meet the criteria for accessing confidential data can obtain the data by contacting the corresponding author of the study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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