Determinants of neonatal Seizure among neonates admitted to neonatal intensive care units in the Awi Zone Hospitals, 2023: A multi-center unmatched case control study.

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Research Article

Keywords: Seizure, neonates, determinants, case control, Ethiopia
Determinants of neonatal Seizure among neonates admitted to neonatal intensive care units in the Awi Zone Hospitals, 2023: A multi-center unmatched case control study.

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ABSTRACT

Background: Neonatal seizure is a common medical emergency that signals severe insult to the neonatal brain. It is a major risk factor for neonatal morbidity and mortality. It has a wide worldwide variation, ranging from 5 per 1,000 live births in the United States of America to 39.5 per 1,000 live births in Kenya. To decrease this significant figure, it is better to investigate its causes further. Therefore, this study aimed to assess its determinants since there was no prior evidence about it in the context of study area.

Objective: Aim to assess the determinants of neonatal seizures among neonates admitted to neonatal intensive care units in the Awi Zone Hospitals, 2023.

Methods: An institution based unmatched case-control study was conducted on 531 admitted eligible neonates from January 1, 2023, to May 30, 2023. A pretested tool was employed to collect data. The collected data were coded, edited, and entered into Epi-data version 3.1 and then exported to SPSS 26. Chi-square and odds ratios were used to assess the relationship between factors associated with the occurrence of neonatal seizure. Model goodness of fit was tested by Hosmer and Lemeshow. Bivariate and multivariate analysis was declared at P<0.25 and P<0.05 respectively to show a significant association with neonatal seizure at a 95% level of significance.

Results: A total of 506 (130 cases and 376 controls) of admitted neonates were used in the final analysis model. Neonates admitted within 24 hours of birth [AOR; 5.98 (95%, CI: 2.18-16.43)], gestational age <32 weeks [AOR; 2.89 (95%, CI: 1.29-6.53)], body temperature >37.5°C [AOR; 4.82 (95%, CI: 1.82-12.76)], blood glucose level < 40g/dl [AOR; 4.95 (95%, CI: 2.06,11.88)], neonatal sepsis [AOR; 2.79 (95%, CI: 1.46-5.35)] and perinatal asphyxia [AOR; 8.25 (95%, CI: 4.23, 16.12)] were found to be determinants of neonatal seizure.

Conclusion and recommendations: In this study, neonatal seizure was determined by the factors of neonatal age, gestational age<32 weeks, body temperature >37.5°C, blood glucose level < 40 g/dl, neonatal sepsis, and perinatal asphyxia. Therefore, the presence of such factors requires prompt recognition and treatment.

Key words: Seizure, neonates, determinants, case control, Ethiopia.
Introduction

Neonatal seizure is clinically defined as a paroxysmal alteration in motor, behavioral, and/or autonomic function due to excess neuronal activity of the neonatal brain(1-3). It is one of the most common overt emergency signs of potentially life-threatening neurological dysfunction in neonates (1-5).

The incidence of seizures varies from nation to nation. It has been reported that 5 per 1,000 live births occurred in the United States of America (6) and 39.5 per 1,000 live births in Kenya (7). The incidence is higher in premature and low birth weight neonates than in term and normal birth weight neonates(6).

Neonatal seizures can cause short-term and long-term effects in neonates. The short term includes higher mortality, prolonged hospitalization, and discharge with neurologic deficits (1, 2). For example, a study conducted in Italy revealed ~16% of patients with neonatal seizures died early, whereas 33% had neurological deficits(8). The long-term effects also includes increased risk of neuro disability among seizure survivors (9-11). For instance, a study reported that ~17– 56% of neonatal patients with seizures developed post neonatal epilepsy (8).

Different studies explained that neonatal seizures are determined by different maternal and neonatal related covariates (1, 2, 7, 12). From this, the most frequent risk factor was hypoxic–ischemic encephalopathy (4), followed by Other factors like neonatal sepsis(7), neonatal age, gestational age, low birth weight and others (13).

Even though neonatal seizure is a public health concern, and a common problem among hospitalized neonates, there has been no prior evidence about its determinants among neonates admitted to NICU in the context of the Ethiopia as well as in the study area. Therefore, this unmatched case control study was done to assess the determinants of neonatal seizures among neonates admitted to neonatal intensive care units in the Awi Zone, public Hospitals.
METHODS

Study area and period

Awi zone is located in the Amhara region, which is 426 km away from the capital city of Ethiopia, Addis Ababa. Based on 2021 census information the zone has a total population of 1,342,324 of whom 51% are females. The zone has a total of 52 health institutions. Of which 47 are health centers, 4 are primary hospitals, and 1 general hospital. All of them (Injibara General Hospital, Agew Gimjabet Primary Hospital, Dangila Primary Hospital, Changi Primary Hospital & Jawi Primary Hospital.) provide neonatal admission services. The study was conducted from January 1/2023– May 30/2023.

Study design

A multicenter unmatched case control study design was conducted.

Population characteristics

Source population

All neonates admitted to Neonatal Intensive Care Units in Awi Zone public Hospitals.

Study population

All neonates admitted to the neonatal intensive care units and fulfilling inclusion criteria in Awi Zone Hospitals during data collection time from January 1, 2023, to May 30, 2023.

Cases: Neonates admitted with the first observation of neonatal repetitive involuntary muscle contractions, abnormal tonic extensions, or jerky movements of any part of the limb, face, or mouth that are not stimulus sensitive and unresponsive to restraining maneuvers or repetitive abnormal chewing, ocular, or pedaling movements at the admission. These include subtle signs such as rolling of the eyes, oral ducal lingual activities, changes in behavior, twitching, and frank convulsion. Finally, it was diagnosed by the ward physician.
**Control:** Are those neonates who didn’t fulfill the diagnostic criteria of neonatal seizures and decision was made after reviewing neonatal chart.

**Eligibility criteria**

**Inclusion criteria for cases**

Neonates admitted to neonatal intensive care units from January 1, 2023, to May 30, 2023, with diagnosis of seizure in the Awi Zone Hospitals and who came with their mothers were included.

**Inclusion criteria for cases**

Neonates admitted to neonatal intensive care units from January 1, 2023, to May 30, 2023, without diagnosis of seizure in the Awi Zone hospitals and who came with their mothers were included.

**Exclusion criteria for cases and controls**

Abandoned neonates and those whose mothers were not mentally competent to be interviewed were excluded.

**Sample size determination and procedure**

**Sample size determination**

The sample size for this study was determined by using a double population proportion formula in the Epi info version 7. By taking determinant variables from previous studies (Apgar score at five minutes, perinatal asphyxia, Preeclampsia, placental pathology, hypoglycemia, and intraventricular hemorrhage) (12). By considering the following statistical assumption of a 95% confidence interval, a four to one allocation ratio of control to case (4:1), and a power of 90%, the maximum sample size was obtained from the variable intraventricular hemorrhage, which gave maximum sample size. The proportion of cases exposed to intraventricular hemorrhage was 30%, and proportion of controls exposed to intraventricular hemorrhage was 15% (12). The calculated sample size was 483. After adding a 10% non-response rate the final sample became 531 with control 398 and 133 cases.

**Sampling procedure**
There are a total of 5 hospitals that provide neonatal intensive care service in Awi Zone. All hospitals were included in the study. The total average of six months neonatal admissions in the selected Hospitals as per the 2021 report was 1142, which was considered as the study population. Then, the sample size was allocated proportionally for each selected Hospitals based on its respective average six months neonatal admission as of 2021 report. For controls, systematic random sampling technique was used, and cases were subsequently included. K value was calculated as \( N/n = 1142/531 = 2 \). Finally, from eligible admitted study populations, controls were selected every 2 intervals by systematic random sampling method until we got a calculated sample size. See Fig. 1.

**Method of data collection**

Data were collected using a structured questionnaire for interviewing mothers in the NICU at admission. The questionnaires have been adapted and modified from different studies conducted in developed and non-developed countries (7, 12, 14, 15). Additionally, a structured checklist adapted from the aforementioned studies was also used to abstract data on some maternal and neonatal determinants of neonatal seizure. Using the checklist, data collectors made observations and measurements. To prevent duplication of neonates referred from the district hospital, a special participant code was written on the referral sheet.

Maternal socio-demographic characteristics, antenatal and intrapartum factors were obtained from direct maternal interviews in the NICU at admission. Moreover, these antenatal and intrapartum factors of neonatal seizure, including maternal medical diseases (hypertension, anemia, ) and gestational-related disorders ( preeclampsia/eclampsia) were examined and crosschecked with respective reports in the neonatal charts, as these factors were often recorded in the chart. Similarly, neonatal risk factors of seizure were obtained from direct maternal interviews and crosschecked with the report in the neonatal charts.

**Operational definitions**

**Neonatal seizure:** is defined as the first observation of neonatal repetitive involuntary muscle contractions, abnormal tonic extensions, or jerky movements of any part of the limb, face, or mouth that are not stimulus sensitive and unresponsive to restraining
maneuvers or repetitive abnormal chewing, ocular, or pedaling movements during the follow-up period. These include subtle signs such as rolling of the eyes, oral buccal lingual activities, changes in behavior, twitching, and frank convulsion (16).

**Cases:** Neonate admitted with clinical signs and symptoms of seizure and confirmed by attending ward physician at the time of data collection.

**Control:** Neonates without signs and symptoms of neonatal seizure or not diagnosed as neonatal seizure by physician at the time of data collection.

**Data processing and analysis**

After checking the completeness of collected data, it was coded, cleaned, and edited at epidata version 3.1. Then, it was exported to SPSS version 26 for data transformation and further analysis. Frequencies, proportion, rates, summary statistics, and cross tabulation were used to describe the study population in relation to relevant variables. Then results were presented in text form, tables, and graphs. Chi-square and odds ratios (OR) were used to assess the association between factors associated with the occurrence of neonatal seizure. The goodness of fit of the final model was checked using the Hosmer and Lemeshow test. Bivariate analysis was first conducted to identify factors that have crude odd ratio of association with neonatal seizure (P<0.25). Using these factors, multivariable analysis was also carried out to identify factors that have significantly adjusted odds of association with developing neonatal seizure (P<0.05) at a 5% level of significance.

**Results**

**Socio demographic characteristics**

A total of 506 (130 cases and 376 controls) neonates admitted to the NICU of hospitals found at Awi zone were included in the final analysis with a response rate of 95.29%. In this current study, the mean age of mothers was 27.72 (SD±5.85), with an age group of 16-46. More than half of the study participants (71) cases and (198) controls were from rural areas. Male neonates accounted for 51.33% of controls and 59.23% of cases from all neonates admitted to the NICU respectively. The mean age of neonates at the time of admission was 3.86(SD±5.66) days. Most of the mothers (96.8%) were married. Regarding maternal occupation, 35.37% of controls and 40 % of cases were farmers, whereas 35.12% controls and 31.54% of cases, 13.03% controls & 13.85% cases and
15.69% controls & 13.85% of cases were housewives, government employed, private employed respectively, and 0.79% were other professions. See Table 1.

**Maternal antepartum, intrapartum, and postpartum-related factors**

Most (95.38%) of the cases and (92.55%) of the controls had ANC follow-ups at nearby health institutions. From this, 58.06% of cases and 57.47% of controls had visited health institutions≥4 times. More than half of the cases 76(58.46%) and 241(64.1%) of controls were multigravida mothers. Of all mothers, 88(17.39%) had a history of bad obstetrics such as abortion, fetal death, and newborn death. Only 60(11.86%) of mothers were diagnosed with preexisting medical conditions and obstetric complications. Most commonly 24(40%) of them were diagnosed with preeclampsia. The duration of labor after the rapture of membrane in 41(31.54) cases and 102(27.13%) controls was less than 18 hours. In the category of mode of delivery, a greater number of cases, 55(42.31) and 256 (68.1%) controls gave birth through SVD. See Table 2.

**Neonatal common medical diagnosis**

The mean birth weight of the study participants was 2709.62gm with SD±709.66gm. More than half of cases (59.23%) and controls (61.44%) were within the gestational age range of 37-42 completed weeks. Almost more than 1/3 of cases were diagnosed with neonatal sepsis 97(28.69%) and nearly 3/4 of controls 241(71.30%) were also diagnosed with neonatal sepsis. Similarly, less than half 59(45.38%) of cases and 71(54.62%) controls were diagnosed with perinatal asphyxia. Nearly 2% of cases and 7% of controls had neonatal jaundice. Out of a total of 51 birth injuries of any type, 11 were cases and 40 were controls. Almost equal number of cases (23) and controls (21) had their random blood glucose level below 40gm/dl. Most of the controls 319(84.84%) had their random blood glucose level between 40 and 125gm/dl. Similarly, 70% of cases had also their random blood glucose level between 40 and 125gmanddl. See Fig. 2.

**Patterns of neonatal seizure**

Out of 130 total seizure cases, the subtle type of seizure accounted for 37.69 %( 49) followed by tonic-clonic 31.54 %( 41), multifocal 25.38 %( 33), clonic 3.08 %( 4), and less than 3% were tonic cases. See Fig. 3.
**Bivariate and multivariate binary logistic regression model for determinants of neonatal seizure**

Within the bivariate logistic regression, the factors that showed significant association with the occurrence of neonatal seizure were sex of the neonate, age of neonate, maternal age, place of delivery, labor duration, newborn type, number of parity, history of antenatal care follow up, number of gravidities, pregnancy-related hypertension, neonatal blood glucose level, neonatal temperature, birth weight, gestational age, neonatal sepsis, neonatal jaundice, and perinatal asphyxia. In the adjusted binary logistic regression model, blood glucose level, neonatal temperature, gestational age, neonatal sepsis, perinatal asphyxia, and neonatal age were only showed significant association.

The odds of developing neonatal a seizure were 5.98 times higher in those neonates admitted within 24 hours of birth as compared to those neonates 7-28 days old [AOR; 5.98(95%, CI: 2.18-16.43)]. Neonates delivered at gestational age <32 weeks had a 2.89 times higher risk of developing neonatal seizure as compared to neonates delivered at gestational age > 37 weeks [AOR; 2.89 (95%, CI: 1.29-6.53)]. The odds of having neonatal seizure were 4.82 times higher for those neonates whose body temperature was >37.5°C as compared to neonates having a normal body temperature [AOR; 4.82 (95%, CI: 1.82-12.76)]. Similarly, neonates with blood glucose level < 40gm/dl were 4.95 times more likely to develop a neonatal seizure than neonates whose blood glucose level was between 40gm/dl and125g/dl [AOR; 4.95 (95%, CI: 2.06,11.88)]. The risk of having a neonatal seizure was 2.79 times higher in the neonates with sepsis as compared to neonates without sepsis [AOR; 2.79 (95%, CI:1.46-5.35)]. Lastly, the odds of occurrence of neonatal seizure among neonates with perinatal asphyxia were 8.25 times higher than its counterpart [AOR; 8.25 (95%, CI: 4.23, 16.12)]. See Table 3.

**Discussion**

This study mainly investigated the determinants of neonatal seizure at five public hospitals in the Awi zone. Using a binary logistic regression model, our investigation assessed socio-demographic, maternal antepartum, intrapartum, postpartum, and neonatal factors.
The odds of developing neonatal seizure were nearly six times higher in neonates admitted within 24 hours of birth as compared to neonates 7-28 days old. This aligns with a study conducted in Landon(17), Kathmandu University in Dhulikhel (18), the University of Gonder in Ethiopia(12), and Dhaka Medical College in India (15). This is because immediately after birth, neonates are challenged with an extra uterine environment, and their organs such as the brain are not completely grown. This makes neonatal brains easily to be provoked when it is exposed to different factors (19, 20).

Neonates delivered at the gestational age < 32 weeks had a 2.89 times higher risk of developing neonatal seizure as compared to neonates delivered at gestational age > 37 weeks. This is consistent with studies conducted in Sweden(21), United States of America (22), and Italy (23). This is because more preterm neonate didn't complete their brain development such as cerebral and cerebellar parts, diminished cortical gyrification, and finally delayed maturation of gray ,and white matter structures, which leads the brain not to function normally (24).

The risk of having neonatal seizure was nearly five folds higher among neonates whose axillary body temperature was greater than 37.5℃ as compared to those neonates whose body temperature is normal. This finding is similar to a study in Iran(25) and Kynea (7). This is because of inflammatory responses outside the central nervous system increase cytokine concentrations in the CNS through neuro-immune network, and the released cytokines in turn trigger neuronal hyper excitability in the central nervous system to generate convulsions(26).

Similarly, neonates with blood glucose level < 40gm/dl were five times more likely to develop neonatal seizure than neonates whose blood glucose level was between 40gm/dl and 125gm/dl. This finding is also in line with studies conducted in Iran(27), India (28). In fact, babies need sugar or glucose for energy and most of the glucose in their body is being used up by their brains. As a result, the brain depends on continuous blood glucose supply as its main source of energy. If severe or prolonged hypoglycemia in a newborn exists, it can cause serious brain injury and the body to convulse(29).
The risk of having a neonatal seizure was 2.79 times higher in the neonates with sepsis as compared to neonates without sepsis. It is consistent with studies in India (28), Kenya (7). This is due to the fact that some infections have ability to damage and passé blood brain barrier that increases the translocation of cytokines, carrying the proinflammatory response from the serum into the brain and favoring seizure susceptibility (30, 31).

Lastly, the odds of occurrence of neonatal seizure among neonates with perinatal asphyxia were 8.25 times higher than its counterpart. Which was consistent with studies in Italy(32), in Ethiopia at university of Gonder (32), India (28). This due to when hypoxia and ischemia occurs, there is a cascade of events that cause a decrease in energy production in the brain. In turn that leads to an increase in an excitatory neurotransmitter called glutamate, which causes excessive activity in the cortex(33).

Limitations
The study might have reduced external validity since controls were not likely to be representative of the source population that produced the cases. The other limitation was the ward physicians only used history and physical examination to diagnose seizure rather than sophisticated investigations like CT scan and EEG which are confirmatory diagnostic tools.

Conclusion and recommendation

The findings of this study indicated that among sociodemographic, maternal and neonatal factors; neonatal age, gestational age<32 weeks, body temperature >37.5°C, blood glucose level < 40g/dl, neonatal sepsis, and perinatal asphyxia were significantly associated with neonatal seizure among neonates admitted to NICU of public hospitals in Awi zone hospitals. Therfoer, health professionals who works in the NICU should better to give priority for those neonates admitted to NICU within 24 hours than others and give close follow up for them. Great attention would also be given for those neonates delivered at gestational age of ≤ 32weeks. Additionally, health professionals should apply aseptic technique during caring neonates. Moreover, it is better to prevent low blood glucose level, fever and perinatal asphyxia.

Abbreviations
ANC: Antenatal Care; AOR: Adjusted Odd Ratios; BT: Birth Trauma; COR: Crude Odd Ratios; NICU: Neonatal Intensive Care Unit; ANC: Antenatal Care; PNA: Perinatal Asphyxia.

Declarations

Ethical approval and consent to participate: This study was conducted after getting ethical clearance from the ethical review committee of Injibara University, College of Medicine and Health Science with protocol number 326/2023. Following the approval, official letters of cooperation was given to the Hospital managers to get permission. After getting permission from them, the mothers were told that the information they gave to be treated with complete confidentiality and didn’t cause any harm. Then informed verbal voluntary assent was obtained from each mother. Moreover, data collectors applied infection prevention techniques such as proper hand washing, gloving, and alcohol rubbing of instruments before touching neonates for the non-maleficent sake of the study.

Consent for publication: Not applicable.

Data availability statement: The data used in this manuscript is available upon reasonable request by contacting the corresponding authors via email.

Competing interest: The authors declare that they have no conflicts of interest.

Funding: No financial funding was received for the study, authorship, and publication of this article.

Author contributions: TA, TDT, BWA TFT and ND substantial contribution to conceptualization, methodology and proposal write up. While, TA, WT, AA, YAM, ZAA, WNM, ZBA and GA and make contribution in data collection, analysis, drafting or revising the article. Finally, we gave final approval of the version to be published, and agree to be accountable for all aspects of the work

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REFERENCE


**Figure Legends**

Figure 1: Diagrammatic presentation of the sampling procedure for the assessment of neonatal seizure among neonates admitted to Neonatal Intensive Care Units in Awi Zone hospitals, Ethiopia, 2023(n=531).

Figure 2: Common medical illness of neonates among neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)

Figure 3: Types of seizure among neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)
Table 1: Socio-demographic characteristics of neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)

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Table 2: Maternal antepartum, intrapartum, and postpartum characteristics of neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)
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<td>137(36.44)</td>
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<td>162(43.09)</td>
<td>7.76(3.26,18.49)**</td>
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<td>1.35(0.87,2.09)*</td>
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<td>≥ 35 years</td>
<td>19(14.62)</td>
<td>63(16.76)</td>
<td>1.00(0.55,1.84)</td>
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<td>Health institution</td>
<td>127(97.69)</td>
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<td>Out of institution</td>
<td>3(2.31)</td>
<td>28(7.45)</td>
<td>3.41(1.02,11.39)**</td>
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Table 3: Bivariate & multivariate logistic regression outputs of neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)
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<th>Gravidity</th>
<th>Parity</th>
<th>Pregnancy-related hypertension</th>
<th>Labor duration</th>
<th>Newborn type</th>
<th>Birth weight</th>
<th>Gestational age</th>
<th>Temperature</th>
<th>Blood glucose</th>
<th>Neonatal sepsis</th>
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<td>Multigravida</td>
<td>65(50)</td>
<td>236(62.77)</td>
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<td>Primigravida</td>
<td>65(50)</td>
<td>140(37.23)</td>
<td>1.69(1.13,2.52)*</td>
<td>0.95(0.35, 2.57)</td>
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<td>Multi para</td>
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<td>267(71.01)</td>
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<td>Primipara</td>
<td>53(40.77)</td>
<td>109(28.99)</td>
<td>1.48(0.99,2.21)*</td>
<td>1.94(0.67, 5.62)</td>
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<td>12(9.23)</td>
<td>12(3.19)</td>
<td>3.05(1.27,7.32)**</td>
<td>1.63(0.49, 5.43)</td>
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<td>Precipitated</td>
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<td>0.88(0.41,1.87)</td>
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<td>Prolonged</td>
<td>12(9.23)</td>
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<td>Two and above</td>
<td>4(3.08)</td>
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<td>0.30(0.11, 0.86)**</td>
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<td>1000-1500gm</td>
<td>2(1.54)</td>
<td>29(7.71)</td>
<td>0.17(0.04, 0.71)**</td>
<td>1.07(0.41,2.79)</td>
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<td>1500-2500gm</td>
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<td>0.67(0.39,1.02)**</td>
<td>0.89(0.46,1.73)</td>
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<td>77(59.23)</td>
<td>230(61.17)</td>
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<td>&lt;32 weeks</td>
<td>30(23.08)</td>
<td>27(7.18)</td>
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<td>2.89(1.29,6.53)**</td>
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<td>32-37weeks</td>
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<td>118(31.38)</td>
<td>0.58(0.35,0.98)**</td>
<td>0.79(0.40,1.55)</td>
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<td>36.5-37.5</td>
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<td>&lt;36.5</td>
<td>96(73.85)</td>
<td>222(59.04)</td>
<td>3.69(1.98,6.88)**</td>
<td>2.19(0.90,3.47)</td>
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<td>&gt;37.5</td>
<td>21(16.15)</td>
<td>43(11.44)</td>
<td>4.17(1.92,9.06)**</td>
<td>4.82(1.82,12.76)**</td>
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<td>40-125g/dl</td>
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<td>&lt;40g/dl</td>
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<td>21(5.59)</td>
<td>3.84(2.03,7.25)**</td>
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<td>Jaundice</td>
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<td>59(45.38)</td>
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<td>6.11(3.84, 9.73)**</td>
<td>8.25(4.23, 16.12)**</td>
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<td>2(1.54)</td>
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<td>0.17(0.04, 0.71)*</td>
<td>0.24(0.05, 1.16)</td>
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</table>

Notice: * p-value <0.25, ** p-value <0.01-0.05, *** p-value <0.01
Figures

**Figure 1**

Diagrammatic presentation of the sampling procedure for the assessment of neonatal seizure among neonates admitted to Neonatal Intensive Care Units in Awi Zone hospitals, Ethiopia, 2023 (n=531).
Figure 2

Common medical illness of neonates among neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)
Figure 3

Types of seizure among neonates admitted to NICU of Awi Zone hospitals from January to May, 2023 (N=506)

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