ORIGINAL RESEARCH ARTICLE

The Effect of Referral Processes and Complications on Survival among Low-Birth-Weight Neonates in the Neonatal Intensive Care Unit of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia: A Retrospective Cohort Study

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ABSTRACT

Background: Low birth weight (LBW) neonates represent a high-risk group for neonatal mortality, particularly in resource-limited settings. Despite national efforts to strengthen referral systems in Indonesia, the impact of referral processes and clinical complications on LBW survival in tertiary NICUs inadequately studied.

Methods: A retrospective cohort study was conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, Eastern Indonesia, involving 319 LBW neonates admitted to the NICU between 2020 and 2023. The primary outcome was 28-day survival. Cox proportional hazards regression was used to estimate crude and adjusted hazard ratios for referral status and clinical complications.

Results: The overall 28-day survival proportion was 61.89%, with peak mortality occurring on days 1 and 3 of life. Extremely low birth weight neonates had the lowest survival (8%). In multivariable analysis, referred neonates had a significantly higher hazard of death compared to directly admitted neonates (HR=1.86; 95% CI: 1.21–2.85; p=0.005). Clinical complications showed a positive but statistically non-significant association after adjustment (HR=2.97; 95% CI: 0.94-9.38; p=0.063).

Conclusion: Referral status was the strongest independent predictor of mortality among LBW neonates. Strengthening pre-referral stabilization, neonatal transport systems, and inter-facility communication is critical to reducing preventable neonatal deaths in Eastern Indonesia.

Keywords: Neonatal Survival, Low Birth Weight (LBW), Referral, Complications, Retrospective Cohort

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Introduction

Health sector development focuses on improving population health and represents a fundamental pillar of the Sustainable Development Goals (SDGs). A key SDGs target is ending preventable deaths of newborns and children under five by lowering the neonatal mortality rate to 12 per 1,000 live births by 2030.[1] Consequently, child health programs emphasize mortality reduction, nutritional improvement, and achievement of minimum service standards for newborns, infants, and children under five.[2]

The neonatal period represents the most critical phase for child survival. Globally, based on WHO and UNICEF data updated in 2025, an estimated 2.3 million newborns died within the first month of life in 2023, or approximately 6,300 deaths daily.[3] In line with SDG targets, in Indonesia, the neonatal mortality rate per 1000 live births has improved by 56 deaths per 1000 live births from 67 in 1953 to 11 in 2023.[4] However, marked regional disparities persist, and the absolute number of neonatal deaths rose from 20,882 in 2022 to 29,945 in 2023.[5]

The main causes of neonatal mortality include low birth weight (LBW) defined as birth weight <2500g, respiratory and cardiovascular, congenital anomalies, infections, neurogical diseases, central nervous system diseases, inpartum complication, unknown cause and other conditions.[2] In Eastern Indonesia, geographic and health system constraints, delayed or suboptimal referrals, and neonatal complications likely contribute significantly to preventable deaths.[6]

Dr. Wahidin Sudirohusodo Hospital in Makassar functions as the primary tertiary referral center for Eastern Indonesia, receiving high-risk neonates from geographically dispersed, resource-limited regions. Long referral distances and unequal NICU distribution make referral a key determinant of LBW survival. In Makassar, 183 neonatal deaths were reported in 2024.[7]

Strengthening the referral system is central to Indonesia's health transformation, particularly in the Eastern region, where neonatal services are being expanded to reduce delays.[8] Despite national efforts, the impact of delayed referral on LBW survival in tertiary NICUs remains under-researched in Indonesia.

Therefore, this study examines the effects of referral processes and clinical complications on survival among LBW neonates in the NICU of Dr. Wahidin Sudirohusodo Hospital, Makassar, as a basis for policy and reduce neonatal mortality.

This study used a separate and independent dataset from our previously published LBW cohort. While previous studies examined maternal factors influencing the survival of LBW neonates, this study included a larger sample size and longer follow-up period, focusing on the referral processes and neonatal complications. Therefore, this study provides new evidence regarding the influence of referral processes and complications on the survival of LBW neonates.[9]

The objective of this study was to estimate the survival proportion, hazard ratios, and the independent effects of referral processes and clinical complications on 28-day survival of LBW neonates admitted to the NICU at Dr. Wahidin Sudirohusodo Hospital, Makassar, using a retrospective cohort design.

Methodology

Study Design: This study was undertaken at Dr. Wahidin Sudirohusodo Hospital, Makassar, using a retrospective cohort design. The primary outcome was 28-day neonatal survival, defined as being alive up to 28 days after birth. The main exposure variables were referral processes (admission via transfer from an external health facility versus direct admission) and the presence of clinical complications, including sepsis and asphyxia, which were recorded as binary variables (present or absent).

Population and Sample: The study population consisted of LBW neonates treated in the NICU of Dr. Wahidin Sudirohusodo Hospital, Makassar from 2020 to 2023, as recorded in the hospital's medical records. A retrospective cohort approach was utilized, with all neonates fulfilling the inclusion criteria throughout the study period enrolled consecutively.

Sample size was calculated based on the formula for comparing two independent proportions, with a significance level of 5% ($Z_{1-\alpha/2}$ = 1.96) and a power of 80% ($Z_{1-\beta}$ = 0.84). Based on the findings of Limaso AA et al[10] (2020), the proportion of neonatal deaths in the exposed group (with complications) was set at P_1 = 0.10 and in the unexposed group (without complications) at P_2 = 0.02, yielding a relative risk of 5.21 and a pooled proportion of P = 0.06. The minimum required sample size was 135 subjects per group (1:1 ratio), giving a total minimum of 270 samples. The final study sample comprised 319 medical records that met the inclusion criteria.

The final sample consisted of 319 LBW neonates, which exceeded this minimum requirement and was therefore considered sufficient to detect statistically significant associations.

The inclusion criteria were LBW neonates (birth weight <2,500 g) who were admitted to the NICU and had complete data on key variables, including 28-day survival status, referral status, and the presence of clinical complications. The exclusion criteria were neonates who were not treated in the NICU, those with incomplete or missing data on essential variables (e.g., birth weight, referral process, survival outcome, or complications), and neonates aged more than 28 days at the time of admission. Missing data were handled using a complete case analysis, whereby only observations with complete information on all variables included in the survival analysis were analyzed. Cases with missing values were excluded prior to analysis.

Data Collection and Analysis This study made use of secondary data derived from medical record sources. Data were collected through a systematic review of the medical records of LBW neonates admitted to the Neonatal Intensive Care Unit (NICU) at Dr. Wahidin Sudirohusodo Hospital, Makassar, between 2020 and 2023. Records that met the inclusion criteria were selected for analysis. Data were analyzed using STATA version 14, encompassing univariate and bivariate analyses, followed by Cox proportional hazards regression modeling to assess the effect of independent variables on low-birth-weight neonates. The proportional hazards assumption was assessed using Schoenfeld residuals with the stphtest command. A global test *p*-value>0.05 indicated that the proportional hazards assumption was satisfied. Retrospective data extraction was performed using a standardized form, with verification procedures applied to reduce potential information bias.

Ethical Approval: Ethical approval for this study was granted by the Health Research Ethics Committee of Hasanuddin University (Approval No. 5164/UN 4.14.1/TP.01.02/2023). Given the retrospective design and the use of secondary data from medical records, the requirement for informed consent was waived by the ethics committee. The confidentiality and anonymity of all participants were strictly maintained throughout the study.

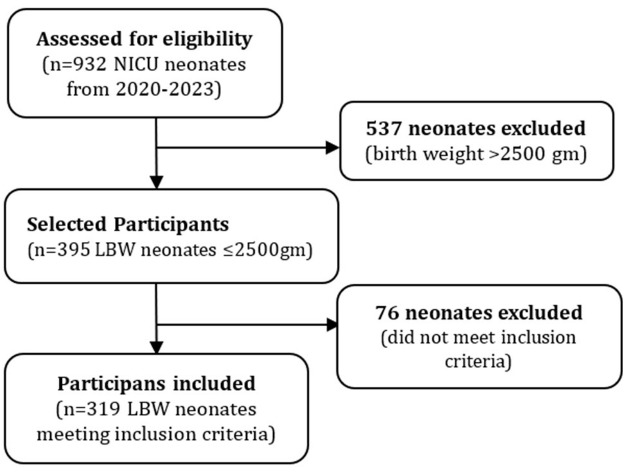

Figure 1: Participant Flow Diagram

Results

Figure 1 presents the participant flow diagram between 2020 to 2023. In total, 932 neonates were hospitalized in the neonatal intensive care unit, of whom 537 were excluded because their birth weight was >2,500 g. The remaining 395 neonates with birth weights ≤2500 g underwent additional screening, of whom 76 were excluded due to failure to meet the inclusion criteria. As a result, 319 low-birth-weight neonates met the eligibility criteria and were included in the final analysis.

Table 1 demonstrates statistically significant differences in birth weight, referral process, and the presence of clinical complications between neonates who died and those who survived ($p < 0.05$). Lower birth weight, referral, and clinical complications were more prevalent in the mortality group. In contrast, sex did not differ significantly between the two groups ($p = 0.343$).

Figure 2 presents that the overall survival proportion of LBW neonates from 2020 to 2023 was 61.89%. Survival decreased markedly within the first week of life, with peak mortality occurring on days 1 and 3.

Figure 3 presents the distribution of LBW neonates by birth weight category, extremely-low-birth-weight (ELBW) neonates experienced the lowest survival proportion, estimated at 8% followed by very-low-birth-weight (VLBW) neonates (56.92%) and LBW neonates (62.41%).

Figure 4 shows that the survival curves stratified by referral process do not intersect, satisfying the proportional hazards (PH) assumption. The log-rank test for the referral process variable yielded a p-value of 0.002, indicating a statistically significant difference in survival between non-referred and referred LBW neonates with referral associated with a higher hazard of death (HR = 1.96; 95% CI: 1.26-2.98). The survival proportion was higher among non-referred neonates (69.64%) compared with referred neonates (46.65%).

Figure 5 shows that the survival curves stratified by diagnosis do not intersect, satisfying the proportional hazards (PH) assumption. The log-rank test yielded a p-value of 0.04, indicating a statistically significant difference in survival between LBW neonates without complication and those with complications (HR = 3.33 ; 95%CI: 1,06-10.50). The survival proportion was higher in the group without complications (76.05%) than in the group with complications (54.26%).

Table 2 shows that the referral process has a statistically significant effect on the survival of low-birth-weight neonates. Neonates admitted via referral had a higher event rate (death) of 40.37%, with a hazard ratio (HR) of 1.94, indicating they were nearly twice as likely to die compared with non-referred neonates. In the bivariate Cox regression analysis, complications were significantly associated with neonatal survival among LBW infants. Neonates with complications had a 3.33-fold higher risk of mortality compared to those without complications (HR = 3.33; 95% CI: 1.06-10.50; $p = 0.040$).

Table 1: Characteristics of Low-Birth-Weight (LBW) neonates

Neonatal Characteristics	Event (Death) (n=116)(%)	Censored (Survived) (n=203)(%)	Total (%)	*P* Value
Birth Weight				0.000
Low Birth Weight (LBW)	54 (46.55)	136 (67.00)	190 (59.56)	
Very Low Birth Weight (VLBW)	39 (33.62)	65 (32.02)	104 (32.60)	
Extremely Low Birth Weight (ELBW)	23 (19.83)	2 (0.99)	25 (7.84)	
Sex				0.343
Male	68 (58.62)	107 (52.71)	175 (54.86)	
Female	48 (41.38)	96 (47.29)	144 (45.14)	
Referral Process				0.002
Not referral	28 (24.14)	73 (35.96)	101 (31.66)	
Referral	88 (75.86)	130 (64.04)	218 (68.34)	
Complications				0.040
Without Complications	3 (2.59)	19 (9.36)	22 (6.90)	
With Complications	113 (97.41)	184 (90.64)	297 (93.10)	

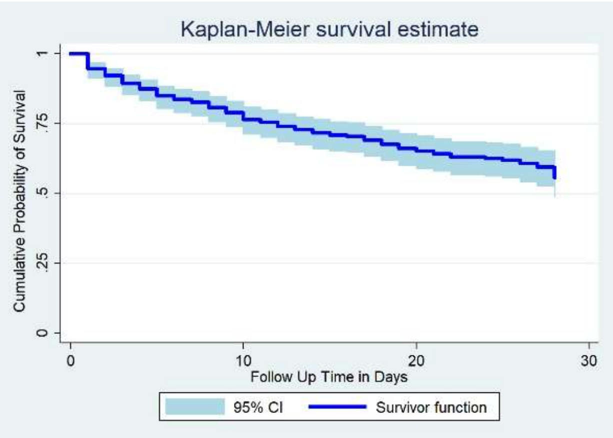

Figure 2: Kaplan-Meier survival analysis of low-birth-weight (LBW) neonates

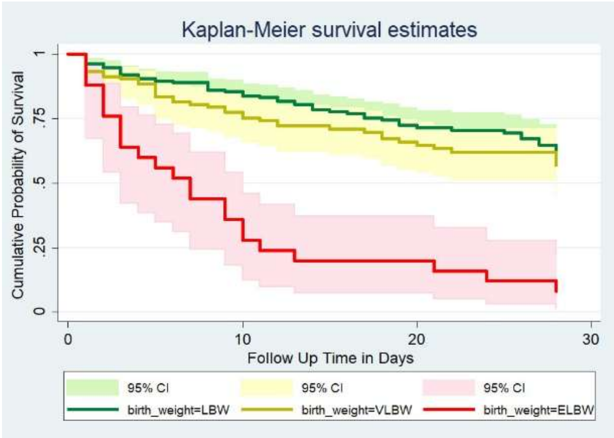

Figure 3: Kaplan-Meier survival curves of low-birth-weight (LBW) neonates stratified by birth weight category

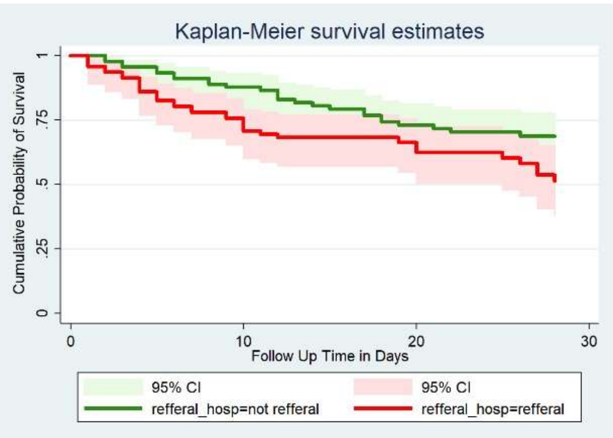

Figure 4: Kaplan-Meier survival curves of low-birth-weight (LBW) neonates stratified by referral status

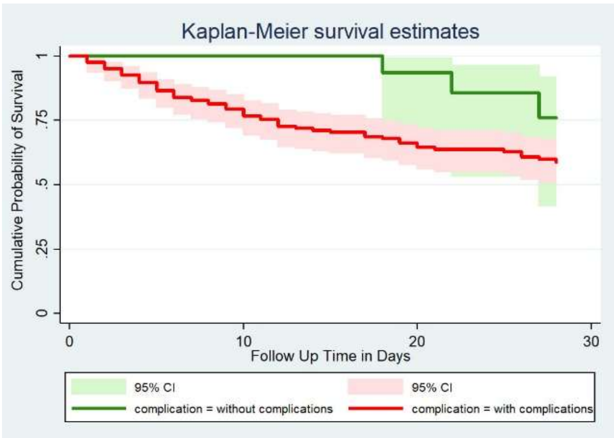

Figure 5: Kaplan-Meier survival curves of low-birth-weight (LBW) neonates stratified by complications

Table 3 presents the multivariable Cox regression results, indicating that referral process was the strongest predictor of mortality among LBW neonates. Referred neonates had a 1.86-fold higher hazard of death than those admitted directly (HR = 1.86; 95% CI: 1.21-2.85; p = 0.005). Conversely, the presence of clinical complications was linked to a higher hazard of mortality; however, this relationship was not statistically significant after adjustment (HR = 2.97; 95% CI: 0.94-9.38; p = 0.063).

In Figure 2, the x-axis represents follow-up time in days, while the y-axis represents the cumulative probability of neonatal survival. The lighter shade band around survival curve indicate the 95% confidence intervals for the survival probabilities.

Table 2: Bivariate cox proportional hazards regression analysis of survival among Low-Birth-Weight (LBW) neonates

Independent Variable	Survival Status		Crude Hazard Ratio (HR)	95% Confidence Interval	*p* Value	Adjusted Hazard Ratio (HR)
	Event (n = 116) (%)	Censored (n =203)(%)				
Referral Process						
Not Referral	28 (27.72)	73 (72.28)	'ref'			'ref'
Referral	88 (40.37)	130 (59.63)	1.94	1.26 - 2.98	0.002	1.88
Complications						
Without complications	3 (13.64)	19 (86.36)	'ref'			'ref'
With complications	113 (38.05)	184 (61.95)	3.33	1.06 - 10.50	0.040	2.95
Sex						
Male	68 (38.86)	107 (61.14)	'ref'			'ref'
Female	48 (33.33)	96 (66.67)	0.84	0.58 - 1.21	0.343	0.81

Table 3: Multivariate cox regression analysis of survival among Low-Birth-Weight (LBW) neonates

Independent Variables	Hazard Ratio (HR)	*p* Value	95% CI
Referral Process	1.86	0.005	1.21 - 2.83
Complications	2.97	0.063	0.94- 9.38

In Figure 3, the x-axis represents follow-up time in days, and the y-axis represents the cumulative probability of neonatal survival. The green line corresponds to low birth weight (1,500-<2,500 g), the yellow line to very low birth weight (1,000-<1,500 g), and the red line to extremely low birth weight (<1,000 g). The lighter shade bands around each survival curve indicate the 95% confidence intervals.

In Figure 4, the x-axis represents follow-up time in days, and the y-axis represents the cumulative probability of neonatal survival. The green line corresponds to non-referred neonates, while the red line represents referred neonates. The lighter shade bands around each survival curve indicate the 95% confidence intervals.

In Figure 5, the x-axis represents follow-up time in days, and the y-axis represents the cumulative probability of neonatal survival. The green line corresponds to neonates without complications, while the red line represents neonates with complications. The lighter shade bands around each survival curve indicate the 95% confidence intervals.

Discussion

The overall survival rate of low-birth-weight (LBW) neonates during the neonatal period (28 days) at Dr. Wahidin Sudirohusodo Hospital, Makassar, was 61.89%. This study showed that referral status remained independently associated with neonatal survival, while complications showed a positive but statistically non-significant association after adjustment (multivariate Cox regression model). Previous studies have shown considerable variation in neonatal survival across settings. Limaso et al. reported a higher survival proportion of 95.9%[11], while other studies reported lower survival proportion, such as those by Woellie et al. (50.9%) and Yismaw et al. (28.8%)[12,13].

The early neonatal period, defined as the first week of life, represents the most vulnerable phase for neonatal mortality.[14-19] This variation likely reflects regional differences in neonatal characteristics and healthcare capacity, including socioeconomic conditions, facility quality, and availability of trained providers. As a referral hospital in Eastern Indonesia, the study site managed neonates with severe complications, such as sepsis, respiratory disorders, asphyxia, and congenital anomalies, which increased mortality risk and challenged survival outcomes.

Low Birth Weight Categories: Mortality differed substantially by birth weight category, with the highest mortality observed among extremely-low-birth-weight (ELBW) neonates. ELBW neonates have immature organs and physiological systems, making them highly vulnerable to respiratory insufficiency, hemodynamic instability, and impaired thermoregulation. These physiological limitations increase the risk of morbidity and mortality during the immediate postnatal period and during transport to the NICU.[20,21] Similar findings indicate a significantly higher risk of death in ELBW and LBW newborns compared with normal weight neonates.[16,22] These findings indicate an inverse relationship between birth weight and neonatal mortality, where lower birth weight is associated with a higher proportion of deaths.[22]

Referral Process: Referral status was significantly associated with neonatal survival. Referred neonates experienced a 1.94-fold higher risk of mortality compared with non-referred neonates, indicating lower survival. This association likely reflects multiple mechanisms, including delayed access to definitive care, prolonged transport times, limited availability of neonatal transport equipment, and suboptimal pre-referral stabilization.

Low-birth-weight (LBW) neonates are particularly vulnerable to hypothermia and hypoxia during transport due to immature thermoregulation, limited energy reserves, thin skin, and a high surface area-to-body weight ratio. Inadequate thermal protection and respiratory support during referral may lead to rapid clinical deterioration. Therefore, the availability of adequate neonatal transport systems and well-trained healthcare personnel is essential to ensure thermal protection and prevent hypothermia during referral.[23]

Consistent with previous studies, referred neonates have a higher risk of mortality than non-referred neonates, likely due to delayed interventions and inadequate initial care.[24] As most neonatal deaths occur within the first 72 hours of life, timely referral and early intervention are critical.[25] Barriers to effective referral often stem from health system limitations, including inadequate facility capacity, limited provider competence, and socioeconomic constraints.[26,27] Strengthening pre-referral care, transportation systems, inter-facility communication, and referral linkages to higher-level facilities is therefore essential to reduce preventable neonatal deaths and improve survival outcomes.[28]

Complications: Neonatal complications were associated with a higher risk of mortality in the bivariate analysis; however, this association was attenuated in the multivariable model, suggesting confounding by other factors. The most common complications observed in this study were neonatal respiratory distress syndrome (39.8%), sepsis (20.4%), congenital anomalies (5.3%), infections (1.9%), and asphyxia (0.63%).

These findings are consistent with previous studies identifying sepsis, respiratory distress syndrome, and asphyxia as major contributors to neonatal mortality. LBW neonates with sepsis have been reported to have more than twice the risk of death[12], while respiratory distress syndrome[16,17,29] and intrapartum-related asphyxia have consistently been identified as strong predictors of neonatal mortality[15,18,22,30-34]. Indonesian studies conducted in Yogyakarta and Bali similarly reported high neonatal mortality attributable to asphyxia and neonatal sepsis, reinforcing the relevance of these complications in the local context[35,36].

Although complications reflect clinical severity, their reduced statistical significance after adjustment suggests that part of their effect may be mediated through referral delays or underlying vulnerability associated with lower birth weight.[36] Nevertheless, the high prevalence of severe complications underscores the need for early detection, prompt management, and intensive supportive care during the intrapartum and early neonatal periods.[25]

Limitations

This study has several limitations. The retrospective design based on medical records is subject to information bias, including potential misclassification of clinical complications due to incomplete documentation. Selection bias is also possible because the study was conducted in a tertiary referral hospital that predominantly manages critically ill neonates, which may overestimate mortality risk. In addition, important confounders, such as gestational age and maternal factors, could not be fully adjusted for. Finally, the single-center design may limit the generalizability of the findings to other healthcare settings.

Strengths

Despite these limitations, this study included a relatively large sample of 319 neonates from the main tertiary referral center in Eastern Indonesia. By integrating clinical and health system perspectives, it provides valuable evidence on the role of referral processes in improving survival among LBW neonates and supports efforts to reduce preventable neonatal mortality.

Conclusion

The overall survival rate of LBW neonates during the neonatal period was 61.89%. In this study, referral status was identified as a key determinant of neonatal survival, with referred neonates experiencing a significantly higher risk of mortality than non-referred neonates (HR = 1.94). In addition, neonatal complications were associated with an increased risk of death in the bivariate analysis, indicating their important clinical contribution to poor outcomes among LBW neonates. The adverse impact of referral and complications likely reflects delayed access to definitive care, prolonged transport times, and suboptimal pre-referral stabilization. LBW neonates are particularly vulnerable to hypothermia and hypoxia during transport due to immature thermoregulation, limited energy reserves, and a high surface area-to-body weight ratio, which may exacerbate the negative effects of inadequate referral practices.

Although neonatal complications were associated with increased mortality in bivariate analysis (HR = 3.33), this association was attenuated after multivariable adjustment, suggesting that their effect may be partially mediated by referral-related factors or underlying vulnerability associated with low birth weight. Nevertheless, respiratory distress syndrome, sepsis, congenital anomalies, infections, and asphyxia remained common and serious contributors to neonatal morbidity and mortality, consistent with findings from other studies.

From a policy perspective, the results underscore the need to strengthen integrated neonatal referral systems. Primary healthcare providers should be trained in the early identification of high-risk LBW neonates and in appropriate pre-referral stabilization, including evidence-based interventions such as kangaroo mother care, thermal protection, airway support, and early infection management. Furthermore, improvements in neonatal transport systems, availability of well-equipped ambulances, and standardized referral communication protocols are essential to minimize delays and ensure continuity of care. Referral hospitals must also maintain readiness in terms of trained personnel, infrastructure, and rapid-response clinical pathways for incoming high-risk neonates.

Future studies should adopt prospective designs to more accurately assess referral delay times, the quality of pre-referral stabilization, and transport conditions, as well as to evaluate the effectiveness of targeted interventions aimed at reducing mortality among LBW neonates. Such evidence will provide a stronger foundation for developing effective policies and clinical guidelines to further improve neonatal survival.

Individual Authors' Contributions: FR contributed to the conceptualization and methodology of the study, conducted the investigation, performed data curation and formal analysis, and was responsible for drafting the original manuscript as well as reviewing, editing, and validating the work. **DR** contributed to conceptualization, methodology, and formal analysis, and was involved in manuscript review and editing, validation of the findings, and overall supervision of the study. **ET** participated in manuscript review and editing, validation of the content, and provided supervisory support. **NA** and **PT** contributed by providing resources and were involved in manuscript review, editing, and validation. **OW** contributed to manuscript review and editing and assisted in validation of the final content.

Availability of Data: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Non-use of Generative AI Tools: This article was prepared without the use of generative AI tools for content creation, analysis, or data generation. All findings and interpretations are based solely on the authors' independent work and expertise.

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