

Co-Morbidities Associated with Prematurity in Two Referral Hospitals in Cameroon

Diomede Noukeu Njinkui^{1*}, Dominique Enyama¹, Yolande Djike Fokam², Cyrelle O. Mefotse Saha³, Beatrice Moudze Kaptue⁴, Charlotte Eposse Koube^{4,5}, Annick A. Tchouamo Sime¹, Christophe Akazong Adjahoung⁶, Marthe E. Barla⁶, Edgar Mandeng Ma Linwa², Seraphin Nguéfack⁷

¹Faculty of Medicine and Pharmaceutical Sciences of the University of Dschang, Dschang, Cameroon

²Faculty of Health Sciences, University of Buea, Buea, Cameroon

³Faculty of Health Sciences, University of Mountains, Bangangte, Cameroon

⁴Douala Laquintinie Hospital, Douala, Cameroon

⁵Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon

⁶Douala General Hospital, Douala, Cameroon

⁷Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

Email: *dnoukeu@yahoo.fr

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Abstract

Introduction: Prematurity is the leading cause of neonatal death in Africa. More than a million children die each year due to co-morbidities related to prematurity. In addition to being one of the causes of neonatal deaths, the health problems associated with prematurity can also lead to severe lifelong impairment in those who survive. **Objectives:** This paper aims to determine the epidemiology and identify co-morbidities of prematurity in the neonatology units of the Douala General Hospital (DGH) and the Laquintinie Hospital of Douala (LHD). **Patients and Methodology:** We conducted an analytical retrospective cohort study from January 2015 to January 2018 in the neonatology department of the DGH and the LHD, which are considered reference hospitals for the management of preterm babies in Cameroon. We included all newborns aged less than 37 weeks admitted to the neonatology units of the DGH and the LHD. The descriptive component was based on the analysis of quantitative variables using measures of central tendency. The analytical component was evaluated using Spearman correlations and the Chi-square and Fisher tests. Simple and multiple logistic regressions measured factors predictive of mortality. The Kaplan Meier survival curve used the Log Rank test and significance at $p \leq 0.05$. **Results:** We recorded 908 preterm newborns in neonatal service and 1,124 preterm deliveries in maternity, representing an incidence of 32.5% in neonatal unit and 10.6% in maternity. 51% of whom were girls, given a sex ratio M/F of 0.9. Hypertension was the main prenatal pathology (9.1%), while premature rupture of membranes: PROM

(35.5%) and eclampsia/pre-eclampsia (18.6%) were the most common obstetrical pathologies. 75.9% of deliveries were vaginal with 65.2% being performed in our referral hospitals. Gestational age ranged from 22 to 36 weeks, with a mean of 32.4 weeks. Late preterm birth rate was 53.7%, and birth weight varied between 590 and 3200 g with an average of 1747 ± 479 g. The percentage of low birth weight (1500 - 2499 g) preterm infants was predominant (65.3%), and the intrauterine growth restriction (IUGR) was estimated to be 12.4%. The majority (96.7%) had pathologies in the neonatal period, the most common being neonatal infection (86.9%). The case-fatality rate was 27.4%, compared to 72.6% live births. Factors influencing mortality are risk of premature labour, gestational age ≤ 32 SA, premature birth in hospitals other than our two referral hospitals, birth weight ≤ 1500 g, Apgar at the 10th minute, late secondary anaemia, hospital resuscitation, oxygen therapy, and duration of hospitalization < 14 days. **Conclusion:** The incidence of prematurity and the mortality rate remains high in neonatal units in Cameroon. Adequate monitoring of pregnancies and management of preterm infants remains a challenge in our context.

Keywords

Epidemiology, Co-Morbidities, Prematurity, Douala

1. Introduction

Prematurity is the leading cause of neonatal deaths in Africa. More than one million children die each year due to premature co-morbidities. The conditions that cause the death of these newborns can also result in severe lifelong disabilities for those who survive. Prematurity is a major public health problem in Africa. It is now an indicator of the health of newborns and a key determinant of infant survival, growth and development. In spite of the many proposed medical care protocols, the incidence of prematurity has varied minimally over the past 40 years. In 1998, Tietche *et al.* estimated the rate of prematurity at 21.05% in the low birth weight unit of the maternity ward at the Yaounde Central hospital [1]. In 2005, Monebenimp *et al.* reported a prematurity rate of 57% at the Yaoundé University Teaching Hospital with a neonatal mortality rate of 35.8% and a perinatal mortality rate of 92% [2]. Publications on comorbidities associated with prematurity in our context are limited. However, the study by Njom *et al.* in Yaoundé in 2014 identified the following as the main comorbidities in very premature babies: apnoea, respiratory distress, neonatal infection, anaemia and neonatal jaundice [3]. We set out to determine the incidence of prematurity and co-morbidities in two referral hospitals in Cameroon.

2. Materials and Methods

Our study was carried out in the neonatology units of the Douala General Hospital (DGH) and the Laquintinie Hospital (LHD) in Cameroon. The neonatal

unit of the Laquintinie Hospital of Douala is classified as a second level hospital in the Cameroon health care structure. However, the neonatal unit of the Douala General Hospital is described as a first grade hospital in the Cameroon health-care structure, receiving the majority of referrals of ill newborns. These two health units each have a maternity unit and receive newborns between the age of 0 to 1 month from their maternity ward and those of other health units in the city of Douala or Cameroon. It was a hospital-based cross-sectional study, with retrospective data collection conducted from 1 January 2015 to 1 January 2018.

All newborns of less than 37 weeks gestational age admitted to the neonatal service of the DGH and HLD were included. Excluded from our study were: Full-term newborns, any inoperable medical record and newborn discharged against medical advice (DAMA).

We collected data from the patient's medical records and the hospital registry, based on a pre-established chart. The parameters collected are sociodemographic data (postnatal age, gestational age at birth, address, socio-economic level of the family), maternal and obstetrical data (maternal age, parity, gestation, obstetrical complications, notion of prenatal corticosteroid), childbirth data (place, type of delivery, duration of amniotic sac rupture, appearance of amniotic fluid, adaptation to extra uterine life and neonatal resuscitation), neonatal pathologies (hyaline membrane disease, apneas, neonatal infections, ulcerative enterocolitis, ...). Data concerning medical care (oxygen therapy, ventilation, antibiotic therapy, phototherapy...) and clinical progress reports (acute complications and lethality). Oxygen therapy was used via oxygen goggles with humidifier, high-concentration oxygen masks or conventional mechanical ventilation, depending on the indication.

Data entry and analysis were performed using Microsoft Excel version 17.2 and the Social Science Statistics package version 20.0.

Inter-variable associations were determined by the Chi² test and the significance level was determined for a value of $p < 0.05$. A bivariate and then multivariate analysis was carried out using the logistic regression method to identify the factors associated with mortality.

The Kaplan-Meier model was used to estimate the survival rate of the study population.

3. Operational Terms

- Early neonatal infection has been defined as an infection occurring less than 7 days after birth.
- Late neonatal infection: infection occurring after 7 days from birth up to 3 months of age.
- No infection: no anamnestic, clinical or paraclinical evidence.
- Possible infection: minor anamnestic criteria, without clinical signs.
- Probable infection: major anamnestic criteria with or without clinical signs.
- Confirmed case of neonatal infection: any newborn under 3 months of age presenting one or more infectious risk factors and/or clinical signs and a

positive culture.

- Extremely preterm: birth at less than 28 weeks of amenorrhoea.
- Very preterm: birth between 28 and 31 weeks' amenorrhoea + 6 days.
- Moderate to late preterm: birth between 32 and 36 weeks' amenorrhoea + 6 days.
- Early secondary anemias: is due to a lack of synthesis and/or response to erythropoietin, the premature baby's low blood cell mass, rapid growth, blood sampling, haemorrhage and infection. The nadir is around 4 to 8 weeks of age, reaching a plateau around 3 to 4 months.
- Late secondary anaemia prevented by iron supplementation of the premature baby.
- Late anaemia is an iron deficiency anaemia, these are caused by low iron and folate reserves built up during the last trimester of pregnancy. It is prevented by systematically prescribing iron and folate on discharge from the neonatal unit.

Bronchopulmonary dysplasia (BPD): This is chronic respiratory failure with persistent oxygen dependence after the 28th day of life in newborns who have presented initial respiratory distress requiring assisted ventilation for at least the first 3 days of life.

4. Results

4.1. Epidemiological and Socio-Demographic Data

During the survey period, 5647 newborns were admitted to the neonatal units of Douala General Hospital and Douala Laquintinie Hospital. Of these newborns, 1833 were preterm babies with an incidence of 32. 5%. 925 were disqualified and we retained 908 subjects for our study (**Figure 1**). Out of the 10620 deliveries in

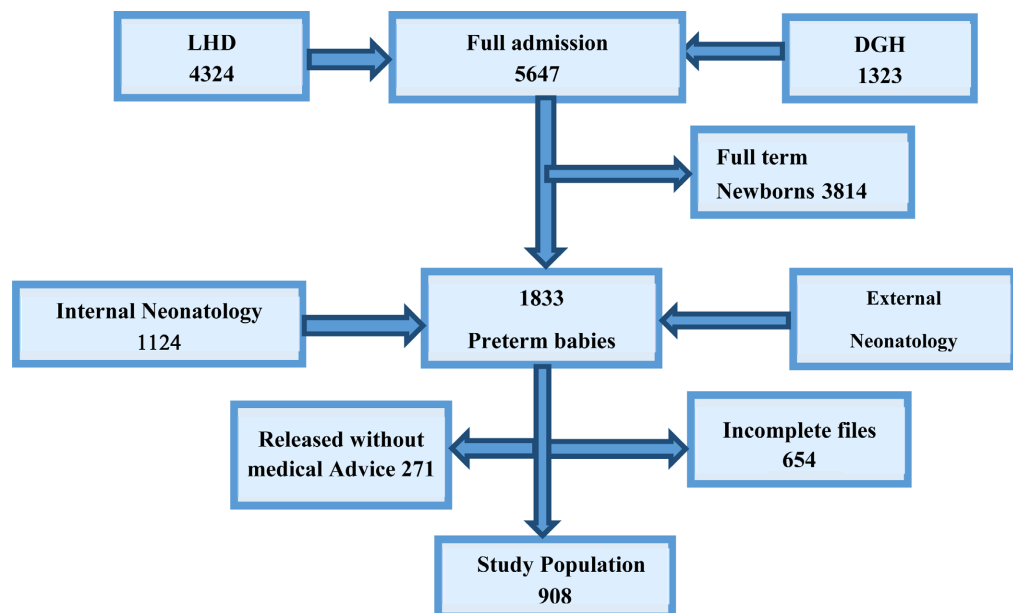


Figure 1. Study population.

the DGH and LHD maternities, 1124 were premature, an incidence of 10.6%. Gestational age was between 22 and 36 weeks, with a mean of 32.4 weeks. By category, extremely preterm babies accounted for only 5.6%, very preterm babies for 40.6%, and moderate to late preterm babies for 53.7% (Figure 2). The majority of newborns were female, with a sex ratio of 0.96. The birth weight of preterm newborns ranged from 590 to 3200 g, with a mean of 1747 g. Low birth weights (1500 - 2499 g) were in the majority with 65.3% (Figure 3). The majority of preterm newborns were eutrophic (85.5%) at birth, 12.4% were hypotrophic. Among hypotrophic preterm infants, 52.9% were asymmetric and 47.1% symmetric hypotrophs.

4.2. Socio-Demographic Data of Mothers

In our study population, the mother's age varied between 14 - 46 years with an average of 28.5 years and the majority of mothers were aged 18 - 35 years (82.2%). 57.9% were unemployed, 56.1% had completed secondary education and 47.9% were multiparous (Table 1).

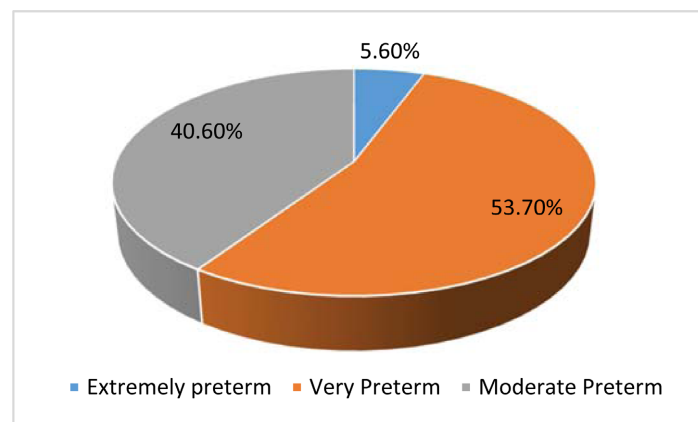


Figure 2. Prematurity by gestational age.

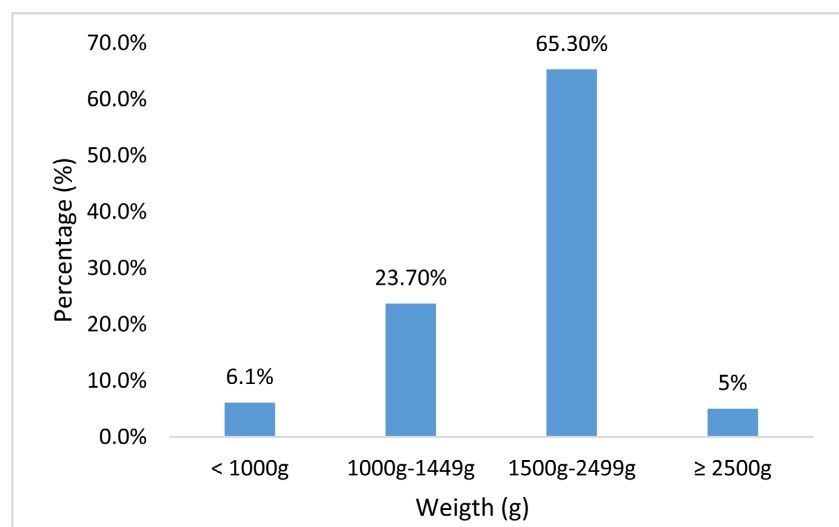


Figure 3. Distribution of premature babies by birth weight.

Table 1. Mother's socio-demographic data.

Variables	Number (n)	Percentage (%)
Mother's age		
<18	34	3.8
18 - 35	745	82.0
>35	129	14.2
Mother's occupation		
Employment	361	42.1
Unemployed	497	57.9
Mother's level of education		
Illiterate	11	2.4
Primary	81	17.9
Secondary	254	56.1
Higher	107	23.6
Parity		
Primiparous	133	14.5
Multiparous	435	47.9
Great multiparity	238	26.2

4.3. Maternal and Obstetrical Data

In our study population, the age of mothers varied from 14 to 46 years, with an average of 28.5 years, and with the majority of mothers between 18 and 35 years of age (82.2%). More than half of the mothers in the study population (61.0%) had a minimum of 3 ANCs. 72.4% had one to three obstetrical ultrasound. Approximately half of the mothers had received prophylaxis for anemia, malaria and tetanus (**Table 2**). Of the 908 participants in the study, 689 (75.9%) had a vaginal delivery.

4.4. Maternal Diseases

Premature rupture of membranes (35.5%) was the most common prenatal condition observed in our study (**Table 3**).

4.5. Neonatal Pathologies and Medical Treatment

Neonatal pathologies were found in 878 preterm newborns (96.7%) and neonatal infection (86.9%) was the most common pathology (**Table 4**).

Nearly half of the preterm babies (44.6%) were kept in an incubator with a source of oxygen. An estimated 177 (19.5%) of the preterm newborns were resuscitated at birth. Almost all preterm babies (96.1%) received antibiotics on admission (**Table 5**).

Table 2. Antenatal monitoring.

Variables	Number (n)	Percentage (%)
Number of ANC		
0	19	3.9
1 - 3	172	35.1
>3	299	61.0
Number of Pregnancy ultrasounds		
0	88	20.3
1 - 3	314	72.4
>3	32	7.4
Prophylaxis		
Tetanus Prophylaxis	446	49.1
Antimalaria Prophylaxis	426	46.9
Iron Prophylaxis	462	50.9

Table 3. Maternal diseases associated with prematurity.

Variables	Number (n)	Percentage (%)
Premature rupture of membranes	322	35.5
Multiple pregnancy	251	27.6
Prolonged rupture of membrane	147	16.2
Malaria	169	18.6
Pre-eclampsia/eclampsia	121	13.3
High blood pressure	83	9.1
PAD	78	8.6
HIV positive	76	8.4
Urogenital infection	35	3.9
Oligohydramnios	25	2.8
Anaemia	17	1.9
Cervical hernia	16	1.8
Diabetes	4	0.4
Asthma	4	0.4
Uterine malformation	3	0.3
Polyhydramnios	2	0.2

Among the 908 preterm newborns admitted during the study period, 249 died during their hospital stay. Extremely preterm and very preterm had lower chances of survival than average prematurity (log rank test $p < 0.001$) (**Figure 4**).

Table 4. Comorbidities present in preterm newborns.

Variables	Number	Percentage
Neonatal pathologies	878	96.7
Respiratory abnormalities	120	13.2
Apneas	99	10.9
Hyaline membrane disease	24	2.6
Liver abnormalities	490	54.0
Jaundice	461	50.8
Vitamin K deficiency	80	8.8
Haematological abnormalities	299	32.9
Early secondary anemias	235	25.9
Late secondary anemias	76	8.4
Digestive abnormalities	79	8.7
Abdominal bloating	66	7.3
Necrotizing enterocolitis (NEC)	21	2.3
Vomiting and/or regurgitation	7	0.8
Gastric residuals	2	0.2
Neonatal infection	789	86.9
Probable Neonatal Infections	735	80.9
Confirmed Neonatal Infections	16	1.8
Neonatal sepsis	44	4.8
Late pathologies	12	1.3
Late anemia	11	1.2
Bronchopulmonary dysplasia (BDP)	4	0.4
Metabolic anomalies	54	5.6
Hypoglycemia	18	3.9
Hyperglycemia	9	1.9

Table 5. Treatment administered to hospitalised preterm newborns.

Variable	Number	Percentage
Medical interventions	873	96.1
Resuscitation at birth	177	19.5
Incubator	405	44.6
Oxygen therapy	397	43.7
Ventilation	150	16.5
Invasive ventilation	4	0.4

Continued

Non-invasive ventilation	148	16.3
Phototherapy	477	49.2
Blood Transfusion	286	31.5
Erythropoietin(Drugs)	27	3.0
Antibiotic therapy	873	96.1

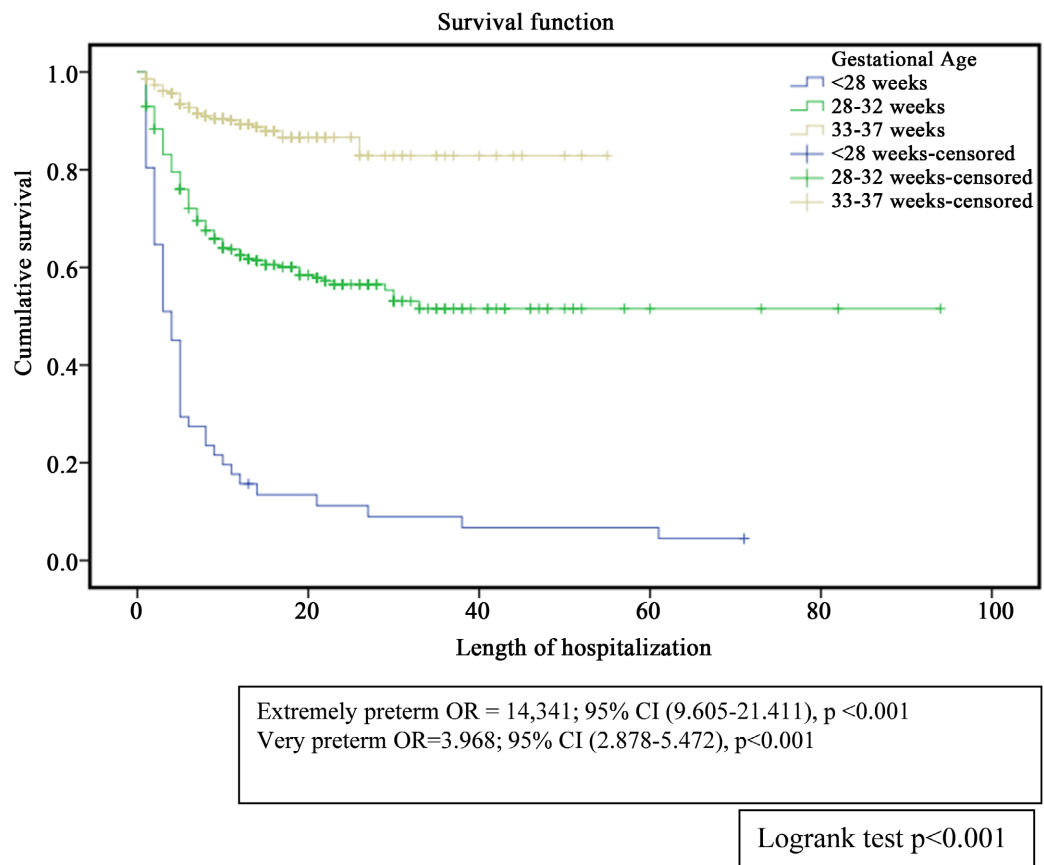


Figure 4. Analysis of surviving premature newborns according to gestational age.

Eclampsia/Pre-eclampsia, hypertension and multiple pregnancies were significantly associated with prematurity ($p < 0.05$) (Table 6).

Threatened preterm delivery, gestational age, premature deliveries in hospitals other than our two referral hospitals, birth weight, Apgar at the 10th minute, late secondary anemia, and resuscitation during hospitalization, oxygen therapy, and duration of hospitalisation < 14 days were independent predictors significantly influencing mortality rates (Table 7).

5. Discussion

Among the 5647 newborns who were admitted to the neonatal units during the study period, we had an incidence of prematurity of 32.5%. Akolly *et al.* in Togo found similar results in a sample of 566 cases [4]. This value is higher than

Table 6. Association between maternal pathologies and gestational age.

variables	Prematurity			P value
	Extreme preterm	Very preterm	Moderate preterm	
Uterine malformation	1 (2.0)	1 (0.3)	1 (0.2)	0.111
Prolonged rupture of membranes	11 (21.6)	68 (18.4)	68 (13.9)	0.118
Premature rupture of membranes	13 (25.5)	137 (37.1)	172 (35.2)	0.263
Urogenital infection	4 (7.8)	9 (2.4)	22 (4.5)	0.093
Malaria during pregnancy	9 (17.6)	71 (19.2)	89 (18.2)	0.917
Pre-eclampsia/eclampsia	1 (2.0)	28 (7.6)	92 (76.0)	<0.001
HIV positive mothers	2 (3.9)	28 (7.6)	46 (9.4)	0.314
Chronic hypertension	1 (2.0)	24 (6.5)	58 (11.9)	0.005
Oligohydramnios	1 (2.0)	15 (4.1)	9 (1.8)	0.136
Threatened preterm delivery	6 (11.8)	38 (10.3)	34 (7.0)	0.160
Anemia during pregnancy	1 (2.0)	6 (1.6)	10 (2.0)	0.902
Cervical insufficiency	2 (3.9)	9 (2.4)	5 (1.0)	0.143
Multiple pregnancy	7 (13.7)	97 (26.3)	147 (30.1)	0.034

Table 7. Independent predictors of mortality in preterm newborns.

Variables	Number		Univariate analysis		Multivariate analysis	
	Survivor	Death	unadjusted OR (95% CI)	P value	OR adjusted (95% CI)	P value
Threatened preterm delivery	47 (7.1)	31 (12.4)	1.851 (1.146 - 2.989)	0.011	16.354 (1.717 - 155.770)	0.015
Gestational age ≤ 32	221 (33.5)	199 (79.9)	0.126 (0.089 - 0.179)	<0.001	15.235 (2.406 - 96.484)	0.004
Neonates from other maternities	215 (32.6)	101 (40.6)	1.409 (1.043 - 1.904)	0.025	5.560 (1.212 - 25.573)	0.027
APGAR 10 th min ≤ 6	22 (4.1)	27 (15.4)	4.278 (2.367 - 7.733)	<0.001	5.468 (5.468 - 24.147)	0.025
Birth weight ≤ 1500 g	116 (17.6)	174 (69.9)	10.860 (7.753 - 15.210)	<0.001	12.286 (6.803 - 22.186)	<0.001
Late secondary anemia	63 (9.6)	13 (5.2)	0.521 (0.281 - 0.964)	0.035	3.941 (1.380 - 11.254)	0.010
Resuscitation during hospitalization	50 (7.6)	127 (51.0)	12.679 (8.665 - 18.552)	<0.001	3.715 (1.401 - 9.853)	0.008
Oxygen therapy	196 (78.7)	8.426 (5.963 - 11.907)	196 (78.7)	<0.001	2.323 (1.032 - 5.230)	0.042
Duration of hospital stay ≤ 14 days	229 (92.0)	6.864 (4.232 - 11.131)	229 (92.0)	<0.001	8.306 (3.887 - 17.748)	<0.001

those found by Tietche *et al.* at the central hospital in Yaoundé (21.05%) in 1998 [5], 8.5% in Nigeria [6], 11.1% and 4.5% in China [7]. This trend is two or three times higher than that observed in developed countries. In Canada, it was 7.5% [8]. In France from 2016 to 2021, the prematurity rate is stable at 7.0% [9]-[11].

The U.S. preterm birth rate declined 1% in 2022 to 10.38%. This 2022 decline follows a 4% rise in the rate from 2020 to 2021 (10.49%) [12]. This can be explained by the fact that the LHD and the DGH are referral centres in the city of Douala and receive several preterm newborns and high-risk pregnancies from other health facilities that lack adequate equipment and qualified personnel for proper medical care. The majority (53.7 %) of preterm newborns are born between 33 and 36 week's gestation, with an average gestational age of 32.4 weeks. Likewise, many authors found similar results [13]-[15]. However, these results are different from those observed by some African authors [16] [17] where very preterm newborns were in the majority because their study population was centred on very preterm newborns. The majority of the premature newborns in our study were low birth weight babies (1500 - 2499 g) and represented 65.3% of the population with an average weight of 1747 g.

Intrauterine growth retardation was associated with prematurity in 12.4% of cases. The IUGR rate associated with prematurity varies in the literature from 16.4% to 96.9% [13] [18]-[20]. The association of prematurity and IUGR is common because the etiologies of these two entities are often complex. In our study, the majority of preterm newborns were female (51%), Tietche *et al.* [5] found a slight female predominance, as did Ndiaye *et al.* [17]. There are no explanations for this slight predominance of the female sex.

Neonatal infection was found in 86.9% of premature newborns, which is close to the findings of Njom Nlend *et al.* [3] who reported the incidence of neonatal infections in 80% of newborns in Cameroon. These results are comparable to the prevalence of neonatal bacterial infections in hospitals, documented by positive blood cultures in similar settings [21]. These figures are very high compared to other African studies. Ndiaye *et al.* had a neonatal infection rate of 64.4% [17]. These differences can be explained by the different criteria (which are not the same) used to diagnose infections. In our context, bacteriological investigations to confirm a possible neonatal infection are occasionally performed because of their high cost, the low socio-economic level of the population and the lack of adequate medical equipment. Antibiotic therapy is sometimes used systematically and wrongly, given the limited availability of diagnostics and the effectiveness of aseptic measures.

Hypothermia was present in 13% of the preterm newborns in our study population on admission. This was less than in the study by Minto'o *et al.* with 56.5% and represents the clinical aspect which is most frequently associated with prematurity on admission to their unit [21]. The study carried out by Ndiaye *et al.* in Senegal found that 62.7% of preterm newborns were hypothermic [17]. In our study, we can relate this low rate of hypothermia to the finding that more than half of the preterm deliveries took place in our maternity units located very close to the neonatal units and thus the referral conditions were adequate.

Liver disorders (jaundice and Vitamin K deficiency) are the second most common co-morbidity associated with prematurity, accounting for 54%. Jaundice rates found in our study are higher than the jaundice rate found by Ugochukwu [22].

The elevated rate of liver anomalies in our study could be explained by the fact that our study exclusively involved preterm newborns who are more likely to develop neonatal jaundice secondary to hepatic immaturity. Hematologic disorders ranked third among co-morbidities with 32.9% represented by early secondary anemia at 25.9% and late onset secondary anemia at 8.4%. These data are similar to the study by Njom Nlend *et al.* with 22% [3]. This can be explained by a low haemoglobin level but also by losses during blood sampling in the first weeks of life. In our study, we observed that only 30.5% of preterm newborns with anaemia have had a blood transfusion and 3% were given erythropoietin. This is attributable to the fact that erythropoietin was not very accessible due to its high cost and that some parents refuse blood transfusions for religious reasons. Respiratory disorders were 13.2%, represented by apnea 10.9% and hyaline membrane disease (HMD) 2.6%. On the other hand, Ikram *et al.* found 38.6% HMD in preterm infants [13], Diouf *et al.* found 16.42% respiratory distress at birth in preterm infants, 43.75% of which was HMD [17]. We can assign this low rate of HMD in our study on the one hand to a diagnostic difficulty since chest X-rays are not performed systematically. On the other hand, there may be an early synthesis of surfactant in the black population (1).

Our study found a mortality rate of 27.4%. Studies carried out in Cameroon revealed a high mortality rate of 37.7% in 2011 and 36.6% in 2013 at the gynaecological-obstetric and paediatric hospital in Yaoundé [23] [24]. In Senegal found 50.3% [17], Lawn *et al.* 27% [25]. The low rate in our study may be due to the fact that its calculation is not based on the overall preterm delivery rate (stillbirths and premature live deliveries not included in our study) but only on the live births included in our study.

Among the risk factors, the threatened preterm delivery was one of the independent predictor of mortality. This may be explained by the fact that expectant women after PROM had not received effective antibiotic treatment nor had they received fetal lung maturation therapy (corticosteroids).

Our study found that gestational age ≤ 32 weeks was a predictor of a preterm death. The mortality rate increased as GA decreased. Ugochukwu *et al.* in Nigeria found a relatively high rate of survivors at 31 to 35 weeks and the majority of deaths at 24 to 29 weeks [22]. Similarly, Ntonya *et al.* in Malawi found a high mortality rate between 24 and 32 weeks and the majority of survivors between 33 and 37 weeks [26]. This situation could be explained by the lack of adequate medical equipment, in particular the accessibility to ventilators and especially by the unavailability of surfactant in our context.

Place of birth was also significantly associated with preterm mortality. The inadequate medical care of the preterm neonate at birth in these hospital services and the ill-adapted conditions of the preterm neonate during their transfer could have contributed to their death during hospitalisation.

The vast majority of preterm newborns who died had a very low birth weight (VLBW). The relationship between weight and prognosis was not proportional. This is similar to studies by several author [8] [23] [24]. Velaphi *et al.* in South

Africa explained that low birth weight preterm infants had low survival rates because they were not on mechanically assisted ventilation and that artificial ventilation is needed in facilities with limited resources to optimize survival [27]. Low-weight babies are at greater risk of death because of their physical, immunological and biological immaturity to maintain and protect against disease.

The Apgar score < 6, was associated significantly and independently with the death of preterm newborns in our study. Tibaijuka *et al.* observed that low Apgar score was a factor in mortality [28]. Given that the Apgar score evaluates the vital parameters of the newborn, the vital functions of preterm newborns are often underestimated and, consequently, their survival is also compromised. Although the Apgar score influenced the outcome of the preterm newborn in our study, it is important to recognize its limitations. Late secondary anemia was the only independent predictor associated with death among co-morbidities. This is because the requirements for optimal medical management of premature newborns in our context and in Africa are not yet sufficient compared to the developing world, hence the need for further rapid improvements.

The need for resuscitation during hospitalization was significantly associated with the demise of preterm newborns. The underlying pathology that triggered resuscitation was severe and contributed to the death of the babies, though a majority survived among those resuscitated.

6. Conclusion

At the end of our study, we can report that the incidence of prematurity during our study period was 32.5% and 10.6% in the Neonatology Units and maternity units respectively. The major comorbidity associated with prematurity was neonatal infection. However, the mortality rate of preterm infants was 27.4%.

Limits

Some missing or incomplete data limit the power of the study. Heterogeneity in practices could result from the 2 study sites and could reduce the comparability of the data.

Authors' Contributions

NDD, ED, and DFY designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. MSCO and NDD designed the data collection instruments and collected the data. ED, NS, and MMLE critically reviewed the manuscript for important intellectual content. NDD, MSCO, and MKB coordinated, and supervised data collection. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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