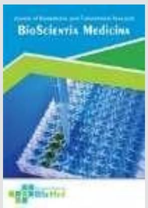
Bioscientia Medicina: Journal Of Biomedicine & Translational Research

eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Risk Factors Affecting Length of Stay in Preterm Infants at Wangaya Regional General Hospital, Indonesia

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ARTICLE INFO

Keywords:
Length of stay
Preterm infants
Risk factors

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v8i1.907

A B S T R A C T

Background: Advances in neonatology have led to many preterm infants being saved. Prolonged length of stay (LOS) increases the incidence of neonatal complications and even mortality, placing a significant economic burden on families and strain on healthcare systems. This study aims to determine the factors associated with LOS in preterm infants. **Methods:** This cross-sectional study involved 60 preterm babies treated at Wangaya Hospital from May 2022 to May 2023. Infants with congenital anomalies, referred from other hospitals and did not receive appropriate treatment were excluded from the study. Data were taken from the electronic medical record after obtaining ethical clearance and then analyzed using descriptive statistics and linear regression in SPSS 25. Statistical significance was considered at 0.05. **Results:** As many as 46 out of 60 preterm infants were born at moderate to late preterm gestational age. The majority of 81.7% of infants were born with a body weight of 1500-2499 grams. The median number of LOS was 7.5 days (IQR 15). Multivariate analysis of numerical independent variables obtained an equation log [LOS] = 2.902-0.066*gestational age+ 0.022*duration of parenteral nutrition (R^2 = 78.1%). Meanwhile, in the categorical independent variables obtained, an equation log [LOS] = 0.398 + 0.223*very preterm + 0.144* RDS + 0.178*NEC + 0.206*prolonged antibiotics administration + 0.278*late enteral feeding + 0.148*abdominal distension + 0.144*vomiting (R^2 = 87.4%). **Conclusion:** Factors influencing LOS of preterm infants are gestational age, duration of parenteral nutrition, the presence of RDS, NEC, vomiting, abdominal distension, late enteral feeding, and prolonged use of antibiotics. It is essential to carry out antenatal care for pregnant women to prevent premature birth.

1. Introduction

Preterm birth is one of the direct causes of neonatal death and accounts for 27% of the 4 million deaths each year throughout the world.[1] Based on the WHO (World Health Organization) report in 2020, it is estimated that there were 13.4 million (9.9%) live births born preterm. South Asia has the highest preterm birth rate of all regions globally, and Southeast Asia ranks third. Nearly 900,000 neonatal deaths resulted from direct complications of preterm birth in 2020.[2] Indonesia is the fifth highest country in the world with the number of preterm births, around 675,700 per year.[3] There is limited data on the mortality of preterm infants in Indonesia. Preterm infants have a high risk of morbidity. Hypoxia, ischemia, mental retardation, seizures, intraventricular hemorrhage, hydrocephalus, microcephaly, hearing and vision impairment, retinopathy of prematurity, respiratory failure, necrotizing enterocolitis (NEC) malabsorption, cholestatic liver disease, sudden infant death syndrome, high blood pressure, and nephrocalcinosis is an early and late complication associated with preterm babies.[4] It causes substantial psychological, physical, and economic costs.[5,6] One of the main factors contributing to costs is the length of hospital stay.

A study showed several factors have a significant effect on the length of stay (LOS) for preterm infants with very low birth weight, including intrauterine growth retardation (IUGR), C-reactive protein (CRP) and positive blood culture, gastric residue containing blood or bile fluid, and the number of days required to regain birth weight.[1] Similar studies have also reported abnormal antenatal umbilical artery doppler, small for gestational age, need for resuscitation, respiratory distress syndrome (RDS), seizures, sepsis, necrotizing enterocolitis (NEC), major congenital malformations, and bronchopulmonary dysplasia (BPD) increased length of stay by 5.4 (3.5–7.4), 21.6 (19–23.9), 4.7 (3.3–6.1), 3 (1.7–4.3), 15.2 (8.5–22.1), 11.2 (9.1–13.2), 9, 8 (5.2–14.4), 8.8 (4.4–13.3) and 5.6 (0.5–10.7) days respectively.[7]

Several studies have discussed the factors influencing the LOS of preterm infants in the NICU or hospital. However, more data should be available regarding these predictive factors in resource-limited countries such as Indonesia. Reducing LOS in preterm infants is crucial to reduce complications, nosocomial infections, cost, and stress levels for parents arising from prolonged hospitalization. Furthermore, reduced LOS in the neonatal intensive care unit (NICU) means more preterm infants can be cared for. This study aims to determine factors related to LOS in preterm infants so that in the future, we can shorten the LOS, thereby increasing the number of preterm infants treated, reducing morbidity and complications that arise due to prolonged stay, which improves the prognosis, reducing economic burden, and stress levels in parents.

2. Methods

This cross-sectional study of 60 preterm infants treated at Wangaya Hospital Denpasar was conducted from May 2022 to May 2023. Preterm infants are defined as babies born with a gestational age of <37 weeks based on the first day of the last period or ultrasound at the beginning of pregnancy if data is missing. Infants with congenital anomalies, discharged against medical advice, referred from other hospitals, and did not receive treatment by the standards of care at our hospital were excluded from the study. The criteria for discharge were breathing room air, tolerating total enteral feeding, and consistent weight gain for three consecutive days. Antenatal steroid administration is a complete dose of dexamethasone 6 mg every 6 hours for two days. The need for resuscitation is giving positive pressure ventilation or compression or administering epinephrine immediately after birth. Prolonged antibiotic administration is defined as giving antibiotics ≥5 days. Late enteral feeding is when a preterm baby begins enteral feeding at ≥72 hours. Meanwhile, prolonged fasting refers to preterm babies without parenteral or enteral nutritional intake for more than 48 hours.

Data was taken from electronic medical records and then analyzed in SPSS 25 using descriptive statistics bivariate and multivariate analysis. A Kolmogorov-Smirnov normality test was carried out. Because LOS data is not normally distributed, we transformed it into log-x form. We used independent T-test formula for bivariate analysis of categorical independent variables (including sex, method of delivery, very preterm, severe SGA, multiparity, multiple pregnancies, RDS, sepsis, NEC, need for resuscitation, prolonged antibiotics administration, late enteral feeding, prolonged fasting, vomiting, abdominal distension, residual volume >50%, blood or bile stained in the NGT, and administration of antenatal steroids). Meanwhile, for independent variables with a numerical scale (including gestational age, birth weight, first-minute Apgar score, fifth-minute Apgar score, time to regain initial birth weight, total enteral nutrition intolerance, and duration of parenteral nutrition) using the Pearson correlation test. Statistical significance was considered at 0.05. The mean difference data and confidence intervals in the table below have been presented by re-transforming log-x into 10^n. All independent and dependent variables with a p-value <0.25 in the bivariate analysis will be included in the multivariate analysis. The statistical test used is predictive linear regression. This research has received approval and passed ethical clearance by the research ethics committee of Wangaya Hospital Denpasar.

3. Results

The total number of preterm infants treated at Wangaya Hospital Denpasar during the study period was 68. Eight patients were excluded from the study; one was discharged against medical advice, four died, and three were referred to tertiary health facilities. Therefore, 60 infants were analyzed in this study. The demographic and clinical characteristics of the samples are summarized in Table 1.

The median number of days hospitalized was 7.5 days (IQR 15). Most infants (73.3%) lived outside Denpasar and were born vaginally (60%). As many as 40 (66.7%) infants were born pretermly due to preterm rupture of membranes. The median gestational age at birth was 33 weeks (IQR 3). Most preterm babies were moderate to late preterm (32 to less than 37 weeks). No infants born at less than 28 weeks gestation survived. Forty-nine (81.7%) infants were born with a 1500 - 2499 grams birth weight. A total of 5 (8.3%) infants were severely small for gestational age (below the 3rd percentile based on the Fenton curve adjusted for sex and gestational age). Only 7 (11.7%) infants received complete antenatal steroid therapy. Other demographic and clinical characteristics of the infants are summarized in Table 1.

Several variables found statistically significant ($p<0.05$), including very preterm (MD 5.24; 95%CI 3.16-8.60), RDS (MD 4.0; 95%CI 2.69-6.16), sepsis (MD 4.14; 95%CI 2.36-7.27), NEC (MD 3.42; 95%CI 1.32-8.89), prolonged antibiotics administration (MD 5.12; 95%CI 3.63-7.24), late enteral feeding (MD 0.16; 95%CI 0.10-0.25), prolonged fasting (MD 5.12; 95%CI 3.46-7.58), abdominal distension (MD 2.81; 95%CI 1.23-6.30), vomiting (MD 2.75; 95%CI 1.65-4.67), gastric residual volume >50% (MD 3.23; 95%CI 1.69-6.16), and blood/bile stained in the NGT (MD 2.75; 95%CI 1.27-5 .88) (Table 2).

Table 2. also provides bivariate analysis data for numerical scale independent variables on length of stay. The correlation between gestational age and birth weight has a Pearson correlation value of -0.755 and -0.692, respectively, which shows a strong negative correlation. Apgar scores in the first and fifth minutes showed a moderate negative correlation. The variable time to reach birth weight has a strong positive correlation, and the number of days of total enteral feeding intolerance and duration of parenteral nutrition have a very strong positive correlation.

After conducting a bivariate analysis, several variables met the criteria for entry into the multivariate analysis. The equation log [LOS] = 2.902-0.066*gestational age + 0.022*duration of parenteral nutrition (R^2 = 78.1%) was obtained using the backward linear regression method. All assumptions of linear regression (i.e., linearity, normality, zero residues, no outlier residue, independence, constant, and homoscedasticity) are met (Table 3). Then, a multivariate analysis was carried out on the categorical independent variables, with the results shown in Table 4. The equation log [LOS] = 0.398 + 0.223*very preterm + 0.144*RDS + 0.178*NEC + 0.206*prolonged antibiotics + 0.278*late enteral feeding + 0.148*abdominal distention + 0.144*vomiting (R2=87.4%) was obtained. All assumptions of linear regression (i.e., linearity, normality, zero residues, no outlier residue, independence, constant, and homoscedasticity) are met.

Table 1. Demographic and clinical characteristics of preterm infants.

Characteristics	Frequency (%)	Median (IQR)
Gender		
Male	34 (56.7)	
Female	26 (43.3)	
Urban	16 (26.7)	
Sectio caesarian	24 (40)	
Location of birth		
Hospital	59 (98.3)	
Primary health center	1 (1.7)	
Causes of preterm termination		
Preterm rupture of membranes	40 (66.7)	
Preeclampsia with severe features	8 (13.3)	
Multiple pregnancies	7 (11.7)	
etc	5 (8.3)	
Multiparous	30 (50)	
Gestational age (weeks)		33 (3)
<28	0 (0)	
28-31	14 (23.3)	
32-37	46 (76.7)	
Birth weight (grams)		
<1000	1 (1.7)	
1000-1499	9 (15)	
1500-2499	49 (81.7)	
≥2500	1 (1.7)	
Severe SGA	5 (8.3)	
Apgar score		
First minute		7 (2)
Fifth minute		8 (2)
RDS	29 (48.3)	
Sepsis	13 (21.7)	
NEC	5 (8.3)	
Requires resuscitation	7 (11.7)	
Prolonged antibiotics administration (≥5 days)	28 (46.7)	
Time of regaining initial birth weight (days)		9.5 (12)
Total enteral nutrition intolerance (days)		2.5 (13)
Duration of parenteral nutrition (days)		4 (14)
Late enteral feeding (≥72 jam)	16 (26.7)	
Prolonged fasting (>48 jam)	22 (36.7)	
Abdominal distension	7 (11.7)	
Vomiting	22 (36.7)	
Gastric residual volume >50%	11 (18.3)	
Bloody or bile-stained in NGT	8 (13.3)	
Antenatal steroid administration	7 (11.7)	
Length of stay (days)		7.5 (15)

Note: IQR= interquartile range; SGA= small for gestational age; RDS= respiratory distress syndrome; NEC= necrotizing enterocolitis; NGT= nasogastric tube.

Table 2. Bivariate analysis of independent variables on the length of stay of preterm infants.

Variables	MD (days)	r	95% CI	p-value
Gender	1.31		0.75-2.24	0.341
Sectio caesarian	0.83		0.48-1.39	0.453
Birth weight		-0.692		<0.001*
Gestational age		-0.755		<0.001*
Very preterm (28-32 weeks)	5.24		3.16-8.60	<0.001*
First-minute Apgar score		-0.464		<0.001*
Fifth-minute Apgar score		-0.484		<0.001*
Severe SGA	0.85		0.31-2.33	0.757
RDS	4.07		2.69-6.16	<0.001*
Sepsis	4.14		2.36-7.27	<0.001*
NEC	3.42		1.32-8.89	0.012*
Need for resuscitation	2.08		0.91-4.93	0.080
Prolonged antibiotics	5.12		3.63-7.24	<0.001*
Late enteral feeding	0.16		0.10-0.25	<0.001*
Prolonged fasting	5.12		3.46-7.58	<0.001*
Multiparous	1.15		0.67-1.99	0.610
Abdominal distention	2.81		1.23-6.30	0.014*
Vomiting	2.75		1.65-4.67	<0.001*
Gastric residual volume >50%	3.23		1.69-6.16	0.001*
Bloody or bile-stained in NGT	2.75		1.27-5.88	0.011*
Multiple pregnancies	1.94		0.83-4.46	0.122
Antenatal steroid administration	2.06		0.89-4.78	0.091
Time of regaining initial birth weight		0.763		<0.001*
Total enteral nutrition intolerance		0.838		<0.001*
Duration of parenteral nutrition		0.852		<0.001*

Note: *significant at p<0.05 in the bivariate analysis; MD=mean difference; r= The Pearson correlation coefficient; CI=confidence interval; p=probability; SGA= small for gestational age; RDS= respiratory distress syndrome; NEC= necrotizing enterocolitis; NGT= nasogastric tube.

Table 3. Multivariate analysis of numerical independent variables on the length of stay of preterm infants.

Parameter	Result	Description
Model	A model consisting of the duration of parenteral nutrition and gestational age variables was obtained.	This model was obtained after the total enteral feeding intolerance, time regaining birth weight, birth weight, fifth-minute Apgar score, and first-minute Apgar score variables were removed from the model, respectively, using the backward method.
Assumption	Linearity: fulfilled	Scatter gives a linear impression
	Normality: fulfilled	Histogram dan P-P plot normal.
	Zero residual means: fulfilled	Mean = 0
	No outliers: fulfilled	Standard residue's minimum and maximum values are -2.393 and 1.697, respectively.
	Constant residue: fulfilled	The graph does not form a specific pattern.
	Independence: fulfilled	The Durbin-Watson value is around 2
	No collinearity: fulfilled	Tolerance >0.4
Regression equation	log [LOS] = 2.902-0.066*gestational age+ 0.022 *duration of parenteral nutrition	
Adjusted R^2	78.1%	The ability of the duration of parenteral nutrition and gestational age to explain the LOS is 78.1%
Correlation coefficient	Gestational age = -0.337	Negative correlation, strength: weak
	Duration of parenteral nutrition = 0.627	Positive correlation, strength: strong
P-value	<0.05	The correlation between each variable gestational age and duration of parenteral nutrition on LOS was statistically significant.

Note: LOS= length of stay.

Table 4. Multivariate analysis of categorical independent variables on the length of stay of preterm infants.

Parameter	Result	Description
Model	A model consisting of NEC, very preterm, vomiting, RDS, abdominal distention, late enteral feeding, and prolonged antibiotics administration variables was obtained.	This model was obtained after the residual volume >50%, sepsis, antenatal steroid administration, prolonged fasting, blood/bile stained in NGT, need for resuscitation, and multiple pregnancy variables were removed from the model, respectively, using the backward method.
Assumption	Linearity: fulfilled	Scatter gives a linear impression
	Normality: fulfilled	Histogram dan P-P plot normal.
	Zero residual means: fulfilled	Mean = 0
	No outliers: fulfilled	Standard residue's minimum and maximum values are -2.413 and 2.630, respectively.
	Constant residue: fulfilled	The graph does not form a specific pattern.
	Independence: fulfilled	The Durbin-Watson value is around 2
	No collinearity: fulfilled	Tolerance >0.4
Regression equation	log [LOS] = 0.398+0.223*very preterm + 0.144*RDS + 0.178*NEC + 0.206*prolonged antibiotics + 0.278*late enteral feeding + 0.148*abdominal distention + 0.144*vomitting	
Adjusted R^2	87.4%	The ability of NEC, very preterm, vomiting, RDS, abdominal distention, late enteral feeding, and prolonged antibiotics administration to explain the LOS is 87.4%
Correlation coefficient	Very preterm = 0.205	Weak positive correlation
	RDS = 0.156	Very weak positive correlation
	NEC = 0.107	Very weak positive correlation
	Prolonged antibiotics administration = 0.224	Weak positive correlation
	late enteral feeding = 0.267	Weak positive correlation
	abdominal distention = 0.104	Very weak positive correlation
	vomiting = 0.151	Very weak positive correlation
P-value	<0.05	The correlation between each variable NEC, very preterm, vomiting, RDS, abdominal distension, late enteral feeding, and prolonged antibiotics on LOS is statistically significant.

Note: RDS= respiratory distress syndrome; NEC= necrotizing enterocolitis; NGT= nasogastric tube; LOS= length of stay.

4. Discussion

Preterm infants have a high risk of morbidity, so they require long hospital stays. This study found factors that were statistically significant related to the length of stay in preterm infants, including gestational age, duration of parenteral nutrition, the presence of RDS, NEC, vomiting, abdominal distension, late enteral feeding, and prolonged use of antibiotics. Gestational age is reported inversely related to LOS of preterm infants.[8-11] A study that estimated LOS based on gestational age reported that LOS decreased as gestational age at birth increased. For every one-week increase in gestational age, the LOS decreases by around 12.1 days.[8] The greater the gestational age is closely related to the more mature the organs, especially the cardiac and respiratory systems, the better the prognosis and the shorter LOS. This study aligns with several previous studies, which found that gestational age was significantly related to LOS (t=-0.337; p<0.05). Overall, gestational age is an essential determinant of LOS for preterm infants in the neonatal ward.

Parenteral nutrition (PN) is given to preterm infants to provide essential nutrition when enteral nutrition is inadequate. Indications for PN in preterm infants include low birth weight, infection, respiratory distress syndrome, patent ductus arteriosus with significant hemodynamic, NEC stage II or higher, surgically treated NEC, late-onset sepsis, metabolic bone disease, and extra-uterine growth retardation (EUGR).[12] PN is started early after birth to bridge the transition from placental nutrition to enteral feeding.[13] Few studies have discussed the relationship between the duration of PN and the length of stay in preterm infants. This study found that the longer the duration of PN, the longer the hospitalization of preterm infants, with a strongly positive correlation coefficient = 0.627.

Longer use of antibiotics is associated with increased length of stay.[14] Exposure to antibiotics in preterm infants has been associated with several adverse effects and obesity later in life.[15] In this study, preterm infants who were given antibiotics for five days or more have longer LOS with MD 5.12 days (95% CI 3.63-7.24). However, when a multivariate analysis was conducted, prolonged antibiotics did not affect the LOS in preterm infants. This study is supported by Murki et al. in 2020.[7] Feeding intolerance in preterm infants refers to the inability to tolerate enteral feeding, a common condition in the NICU. This condition is characterized by symptoms such as gastric residual volume, abdominal distension, gastrointestinal symptoms (vomiting, blood in vomit, blood in the stool), and other diagnostic tests. The prevalence of feeding intolerance in preterm infants varies from 15% to 30%.[16] Feeding intolerance is often associated with NEC and sepsis and with hematological changes, such as a decrease in platelet count and an increase in the ratio of immature neutrophils to total neutrophils (I/T ratio).[17] The gut microbiome has also been implicated in feeding intolerance, with differences in gut flora composition observed between infants with feeding intolerance and those with feeding tolerance.[18] Several studies have reported that preterm infants with food intolerance have a longer hospital stay.[19] Other studies add that enteral feeding intolerance in preterm infants will cause complications such as a longer duration of parenteral nutrition, nosocomial infections, and hepatic dysfunction, thus causing an increase in LOS.[20] This study confirmed other previous studies that enteral feeding intolerance has a very strong positive correlation with LOS in preterm infants ($r = 0.838$, $p<0.05$).

Several symptoms manifest enteral feeding intolerance, such as abdominal distension, vomiting, gastric fluid retention, and blood and bile in the NGT.[21] Due to an immature digestive system, feeding intolerance prolongs the time to achieve total enteral feeding, thereby prolonging the duration of parenteral nutrition and the length of hospital stay. In this study, among the factors influencing feeding tolerance, late enteral feeding, vomiting, and abdominal distension greatly influence LOS in preterm infants. This research is supported by Tyson et al., who reported a 42% reduction in the duration of hospitalization after early enteral feeding and good enteral feeding tolerance.[22] In addition to shortening the length of hospital stay, early initiation of enteral feeding reduces morbidity and the risk of sepsis. Trophic feeding can increase feeding tolerance and reduce the time needed for total enteral feeding without parenteral nutrition. A meta-analysis study reported that early enteral feeding did not increase the incidence of NEC with a typical risk ratio of 1.07 (95% CI 0.67-1.70); risk difference 0.01 (-0.03-0.05).[23] In this study, late enteral feeding was positively correlated with the LOS in the hospital.

Previous studies have reported an association between NEC and LOS in preterm infants. Infants with NEC who required surgery had a longer LOS than controls, with an increase in the average LOS of 60 days.[24] Infants with NEC treated only with medication also had a longer LOS (an increase of 22 days).[25] In this study, there were five preterm patients with NEC, and no cases of NEC required surgery. From the multivariate analysis, it was found that NEC influenced LOS ($r=0.107$). Increased LOS for infants with NEC contributes to higher hospital costs. This study also confirmed that RDS in preterm infants is associated with a longer LOS in the hospital ($r=0.156$). RDS is a common cause of respiratory morbidity and mortality in preterm infants, and it is caused by a lack of pulmonary surfactant due to fetal lung immaturity.[26] Infants with RDS often require respiratory support, such as mechanical or non-invasive ventilation, which can prolong their hospital stay.[27] Additionally, the severity of RDS can impact the length of stay, with more severe cases requiring longer hospitalization.[28] It has been found that preterm infants with severe RDS who require mechanical ventilation have increased cortisol levels, indicating a higher stress level associated with respiratory distress.[29] Therefore, the presence and severity of RDS in preterm infants can contribute to a longer LOS.

Among perinatal factors, SGA was reported to have the most significant influence on LOS, which is 21 (19-23) days. SGA is closely related to infant mortality and morbidity. Research by Qui et al. reported that SGA in <33 weeks infant increases the risk of mortality, NEC, BPD, and ROP, requiring more extended respiratory support and increased length of stay.[30] However, in this study, SGA does not affect the length of hospital stay. This is because the incidence of SGA is small, and the average gestational age is ≥33 weeks, so it is less representative. Antenatal steroid administration has been shown to improve the prognosis of preterm infants. Antenatal steroids effectively prevent RDS and reduce the need for intensive care.[31] Antenatal steroid therapy, even with incomplete doses, has also been proven to reduce the incidence of RDS and death.[32] However, this study found that giving complete antenatal steroids was not associated with LOS (p-value = 0.09). A previous study supports this study.[7] Further research is needed with a larger sample and controlling more confounding variables.

5. Conclusion

Gestational age, parenteral nutrition duration, RDS, NEC, vomiting, abdominal distension, late enteral feeding, and prolonged use of antibiotics influenced the LOS of preterm infants. It is essential to carry out antenatal care for pregnant women to prevent premature birth. The authors advise clinicians to use this study's results in estimating the LOS for preterm infants with several risks. Suggestions are also given to future researchers to do the study with a larger sample, therefore better represent the population.

6. References

1. Niknajad A, Ghojazadeh M, Sattarzadeh N, Bashar HF, Dezham SF. Factors affecting the neonatal intensive care unit stay duration in very low birth weight premature infants. J Caring Sci. 2012; 1(2): 85-92.
2. World Health Organization. Born too soon: decade of action on preterm birth. Geneva: World Health Organization. 2023.
3. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379: 2162-72.
4. Kliegman RM, Stanton B, Geme JS, Schor N, Behrman RE. Nelson Textbook of pediatrics: expert consult premium edition - enhanced online features and print. Philadelphia: Elsevier. 2011.
5. Zhang M, Wang YC, Feng JX, Yu AZ, Huang JW, Jiang SY, et al. Variations in length of stay among survived very preterm infants admitted to Chinese neonatal intensive care units. World J Pediatr. 2022; 18(2): 126-34.
6. Flacking R, Lehtonen L, Thomson G, Axelin A, Ahlqvist S, Moran VH, et al. Closeness and separation in neonatal intensive care. Acta Paediatrica. 2012; 101: 1032–7.
7. Murki S, Vardhelli V, Deshabhotla S, Sharma D, Pawale D, Kulkarni D, et al. Predictors of length of hospital stay among preterm infants admitted to neonatal intensive care unit: Data from a multicentre collaborative network from India (INNC: Indian National Neonatal Collaborative). J Paediatr Child Health. 2020; 56(10): 1584-9.

8. Seaton SE, Draper ES, Adams M, Kusuda S, Håkansson S, Helenius K, et al. Variations in neonatal length of stay of babies born extremely preterm: an international comparison between iNeo networks. The Journal of Pediatrics. 2021; 233: 26-32
9. AlJohani E, Mostafa Q, Al-Matary A. Estimating the neonatal length of stay for preterm babies in a Saudi tertiary hospital. Journal of Clinical Neonatology. 2020; 9(1): 13.
10. Seaton SE, Barker L, Draper ES, Abrams KR, Modi N, Manktelow BN. Estimating neonatal length of stay for babies born very preterm. Archives of disease in childhood-fetal and neonatal edition. 2019; 104(2).
11. Seaton SE, Draper ES, Abrams KR, Modi N, Bradley, Manktelow BN. Can we estimate the length of stay of very preterm multiples?. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2019; 104(5).
12. Wang Y, Shen W, Yang Q, Lin R, Tang L, Bai R, et al. Analysis of risk factors for parenteral nutrition-associated cholestasis in preterm infants: a multicenter observational study. BMC Pediatrics. 2023; 23(1): 250.
13. Mihatsch W, Varas MA, Diehl LL, Carnielli VP, Schuler R, Gebauer C, et al. Systematic review on individualized versus standardized parenteral nutrition in preterm infants. Nutrients. 2023; 15(5): 224.
14. Sourour W, Sanchez V, Sourour M, Burdine J, Lien ER, Nguyen D, et al. The association between prolonged antibiotic use in culture negative infants and length of hospital stay and total hospital Costs. American Journal of Perinatology. 2021; 40(5): 525-31.
15. Fajardo C, Alshaikh B, Harabor A. Prolonged use of antibiotics after birth is associated with increased morbidity in preterm infants with negative cultures. Journal of Maternal-fetal & Neonatal Medicine. 2019; 32(24): 4060-6.
16. Weeks CL, Marino LV, Johnson MJ. A systematic review of the definitions and prevalence of feeding intolerance in preterm infants. Clinical Nutrition. 2021; 40(11): 5576-86.
17. Alhamad MM, Kumar A, Chaaban H, Wickline KM, Ho TT. Platelets and immature neutrophils in preterm infants with feeding intolerance. American Journal of Perinatology. 2021; 38(11): 1150-7.
18. Li Y, Jia C, Lin X, Lin L, Li L, Fan X, et al. The diversity of the intestinal flora disturbed after feeding intolerance recovery in preterm twins. Front Pediatr. 2021; 10(9): 648979.
19. Ojha S, Mitchell E, Montgomery A, Dorling J, Meakin G, Culshaw L, et al. Full milk feeding from day one for preterm infants. Infant. 2020; 16(1): 26-9.
20. Patton L, de la Cruz D, Neu J. Gastrointestinal and feeding issues for infants <25 weeks of gestation. Semin Perinatol. 2022; 46(1): 151546.
21. Huang X, Chen Q, Peng W. Clinical characteristics and risk factors for feeding intolerance in preterm infants. Journal of Central South University. 2018; 43(7): 797-804.
22. Tyson JE, Kennedy KA. Trophic feedings for parenterally fed infants. Cochrane. 2005; 20(3).
23. Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane. 2013; 28(3).
24. Sun J, Marwah G, Matthew, Westgarth M, Buys N, Ellwood D, et al. Effects of probiotics on necrotizing enterocolitis, sepsis, intraventricular hemorrhage, mortality, length of hospital stay, and weight gain in very preterm Infants: a meta-analysis. Advances in Nutrition. 2017; 8(5): 749-63.
25. Chi C, Buys N, Li C, Sun J, Yin C. Effects of prebiotics on sepsis, necrotizing enterocolitis,

mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis. European Journal of Clinical Nutrition. 2019; 73(5): 657-670.

26. Rahmawati E, Anggraeni MD, Setiyowati E. Cesarean delivery and respiratory distress syndrome in late preterm infants. Indonesian Journal of Nursing Science. 2020; 2(2): 38-43.
27. Kim Y, Kim Y, Chang M, Lee B. Association between thyroid function and respiratory distress syndrome in preterm infants. Pediatric Reports. 2022; 14(4): 497-504.
28. Gabr HE, Fouad MA. Antenatal steroid in preterm infants with respiratory distress syndrome. The Egyptian Journal of Hospital Medicine. 2022; 88(1): 3249-54.
29. Lai SH, Xie YL, Chen ZQ, Chen R, Cai WH, Wu LC, et al. Non-invasive high-frequency oscillatory ventilation as initial respiratory support for preterm infants with respiratory distress syndrome. Front Pediatr. 2022; 9.
30. Qiu X, Lodha A, Shah PS, Sankaran K, Seshia MM, Yee W, et al. Neonatal outcomes of small for gestational age preterm infants in Canada. Am J Perinatol. 2012; 29(2): 87-94.
31. Akhtar N, Singh P, Shahrukh N, Haider A. Antenatal rescue corticosteroids and perinatal outcome. Int J Reprod Contracept Obstet Gynecol. 2021; 10(6): 2312-15.
32. Metaferia G, Abayneh M, Aynalem S, Demisse AG, Demtse AG, Eshetu B, et al. Antenatal steroid utilization in Ethiopia. Glob Pediatr Health. 2021; 8: 1-8.