Review Article:

Mortality and Morbidity Patterns of Very Low Birth Weight Newborns in Eastern Mediterranean Region: A Meta-Analysis Study

Fatemeh Nayeri[1], Zahra Emami[1], Yasamin Mohammadzadeh[2], Mamak Shariat[1], Setareh Sagheb[2], Leyla Sahebi[1*]

1. Maternal, Fetal, and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran.
2. Breast Feeding Research Center, Tehran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Context: Preterm and low-birth weight are of the most common causes of mortality and critical disabilities in newborns. Although advances in neonatal care improved survival and quality of life in the developed countries, mortality and morbidity due to prematurity are still high in the developing and underdeveloped countries such countries in Eastern Mediterranean Region (EMR).

Objective: The study aimed at evaluating mortality and morbidity among Very Low Birth Weight (VLBW) and Very Preterm (VP) neonates in EMR.

Data Sources: A systematic search was conducted in CINAHL, Cochrane Library, Current Contents, Database of Abstracts of Reviews of Effects (DARE), Google Scholar, PubMed, PsycINFO, Thomson Reuters, Scientific Information Database (SID), and Medical Library (MedLib) as well as regional WHO database to detect relevant studies published from 1996 to 2016.

Study Selection: English Language Literature From EMR countries, which reporting outcomes of VLBW and VP were considered. Finally, 32 full text articles were included.

Data Extraction: Data on VLBW and VP outcomes including mortality, and short- and long-term morbidities were extracted.

Results: Meta-analysis results of prevalence of mortality among VLBW newborns was obtained as 32.0%, which was different from Asian and African countries (23% vs. 55%). Pooled odds ratio of mortality among VLBW newborns was estimated as 2.41. The most prevalent comorbidity in VLBW and VP newborns were allocated to septicemia and Neurodevelopmental Delay (NDD), and the rarest belonged to Periventricular Leukomalacia (PVL) and Necrotizing Enterocolitis (NEC). The main limitation of the current study was lack of relevant studies and adequate sample size.

Conclusions: It seems that indicators in EMR should be evaluated independently in Asian and African countries. Septicemia, as relatively curable cause of morbidity, is the most prevalent comorbidity among VLBW infants.

** Corresponding Author:*
Leyla Sahebi, PhD.
Address: *Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran.*
Tel: *+98 (21) 61192631*
E-mail: *sahebileila@yahoo.com*

1. Context

Neonatal mortality is one of the major global health concerns to such an extent that 45% of total mortalities in children less than five years occur in neonatal period (1). Very Preterm (VP) and Very Low Birth Weight (VLBW) are defined as gestational age <32 weeks and birth weight <1500 g, respectively (1). Preterm birth and Low-Birth Weight (LBW) are the most common causes of newborn mortality. In addition, survived preterm infants are compromised to lifelong disabilities, such as major neurodevelopmental disorders, intellectual disability, hydrocephaly, as well as visual and hearing impairments (2-7).

Most of the VP and VLBW infants need advanced neonatal cares to survive. Although advances in neonatal care have improved their survival and quality of life in the developed countries, VP and VLBW morbidity and mortality are still at their peak in the developing and underdeveloped countries (8). In high-income countries, 95% of preterm babies survive, of which 90% develop no impairments, but in many low-income countries, almost all of the VP births die from lack of basic cares (9). On the other hand, most of the middle-income countries suffer from long-term consequences and disabilities caused by preterm births, especially extremely preterm births (10).

Overall, limited studies have been conducted on the outcomes of VLBW in infants. In addition, they also assessed a few types of morbidity. According to the World Health Organization (WHO), Eastern Mediterranean Region (EMR) mostly includes the middle- and low-income countries, and in spite of the importance of the study subject, no review study was conducted in this region. Therefore, there is a paucity of comprehensive studies on the outcomes of VP and VLBW in EMR countries.

2. Objective

The current study aimed at reviewing the morbidity and mortality of prematurity among VP and VLBW infants in EMR countries. Also, the study compared morbidity and mortality rate among infants born weighing <1500 to ≥1500 g. The authors believe that the current meta-analysis can help have an insight of the prematurity problem in this region and clarify life-threatening outcomes under similar situations.

2.1. Inclusion criteria

All the articles published in English on outcomes of VP and VLBW (morbidity and mortality) in EMR countries from January 1996 to December 2016 were entered into the study.

3. Data Sources

The current study used web-based citation index to cite manuscripts of these identified articles. All the articles published from January 1996 to December 2016 as well as their reference lists were searched in order to extract relevant studies. The authors made a direct contact with some other authors from various EMR countries. Searching was conducted from September to December 2016.

3.1. Search strategies

The authors searched CINAHL, Cochrane Library, Current Contents, Database of Abstracts of Reviews of Effects (DARE), Google Scholar, PubMed, PsycINFO, Thomson Reuters, Scientific Information Database (SID), Medical Library (MedLib), and regional WHO database to detect relevant studies.

Medical Subject Heading (MeSH) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) database were also used for terms and keywords. The following MeSH terms were used in the current study as keywords: (Preterm OR very preterm OR premature OR very premature OR low-birth-weight OR very-low-birth-weight immature) AND (infants OR newborns OR neonates) AND (mortality OR survival OR morbidity OR outcome OR follow-up) in combination with EMR countries names, including Afghanistan, Bahrain, Djibouti, Egypt, Iran (Islamic Republic of), Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen.

4. Study Selection

To find articles reporting mortality and or morbidity of VP and or VLBW in EMR countries, a literature search was performed on observational and analytical studies, published in peer-reviewed journals from 1996 to 2016. The search strategy was developed and studied by all authors.

Publications would be included in the study if 1. They were published in English language from January 1996 to December 2016; 2. Reported outcomes of VP/VLBW

including mortality, short- and long-term morbidities; and 3. Had reports statistics from EMR countries. Studies would be excluded if they contained no data on above-mentioned outcomes, not reported data from EMR countries, systematic reviews with no direct data on required information, and case studies with sample sizes less than 15 subjects. In addition, publications reporting overall neonatal mortality or morbidity rate, without subcategories of gestational age or birth weight were excluded. Eligible studies were reviewed to recheck relevancy and accordingly, related data were excluded.

5. Data Extraction

Two reviewers extracted data based on data extraction template of the Cochrane consumers and communication review group. The pilot study was conducted on eight randomly-selected articles. One review author extracted the related data from included studies and the second author checked the accuracy of extracted data. Extracted data elements comprised study year, study design, geographical location, sample size, participants, inclusion criteria, predicted outcomes, type of statistics, and analysis method. Disagreements were resolved by a third or fourth author. Studies with duplicate citations and those conducted on certain subpopulations were excluded.

5.1. Data items

The primary outcome was prevalence and odds ratio of mortality among VLBW/VP newborns. Secondary outcomes included prevalence and odds ratio of morbidity from Respiratory Distress Syndrome (RDS), Bronchopulmonary Dysplasia (BPD), pneumothorax, pulmonary hemorrhage, Retinopathy of Prematurity (ROP), Intraventricular Hemorrhage (IVH), Periventricular Leukomalacia (PVL), Necrotizing Enterocolitis (NEC), Patient ductus Arteriosus (PDA), asphyxia, congenital anomalies, sepsis and Neurodevelopmental Delay (NDD) or Psychomotor Development Retardation (PDR), speech delay, Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive-Compulsive Disorder (OCD), and possibly seizures.

5.2. Risk of bias in case studies

The reviewers evaluated the risk of bias in the current review study. Risk of bias was checked by the Cochrane collaboration tool.

5.3. Summary measures

Pooled ratio of mortality and morbidity from various disorders and receiving surfactant, mechanical ventilation, or CPAP (Continuous Positive Airway Pressure) among VLBW and VP newborns were calculated by random-effects models; pooled odds ratio also was calculated by meta-regression analysis. All analyses were conducted with STATA 14 (Stata Corp. 2014. Stata Statistical Software: Release 14. College Station, TX: Stata Corp LP).

5.4. Study analyses

Heterogeneity and meta-regression were investigated by subgroups of the study year (before 2006 vs. after 2007), type of design (cross sectional study vs. other designs), sample size (<200 and >201), and countries (Asian vs. African countries).

5.5. Risk of bias across studies

The bias findings for prevalence and odds ratio of mortality in VLBW neonates are shown in funnel plots (Figures 1, 2).

6. Results

Initial search identified 1339 titles. After removing duplications, the remaining 1307 titles and abstracts were screened. Overall, te full-text of 117 screened studies were selected and reviewed. Finally, 32 full-texts were reviewed and analyzed to extract data (Figure 3). Overall, 9 study had reported mortality among VLBW newborns (11-19) (Figure 1).

The basic characteristics of studies reviewing mortality and morbidities among VLBW/VP newborns are shown in Tables 1 and 2. Considering the prevalence of mortality among VLBW newborns, the highest and lowest levels in the Middle-East were 60.0% in Egypt (12) and 14.0% in EUA (16). Unfortunately, information about prevalence of VP infants was not accessible in the studies. Meta-analysis of prevalence of mortality among VLBW newborns were 32.0% (95%CI: 27.0-38.0; $P_{heterogeneity}$=0.00) (Figure 4).

In the meta-regression analysis, the prevalence of mortality among VLBW newborns was not heterogeneous based on the study design (meta-analysis of prevalence of mortality in cross-sectional studies=40.0% [95%CI:28.0-51.0] vs. other designs=26.0% [95%CI: 17.0-35.0], $P_{heterogeneity}$=0.074) and year of study (before 2006=46% [95%CI: 20-72] vs. after 2007=26% [95%CI: 19-33], $P_{heterogeneity}$=0.137).

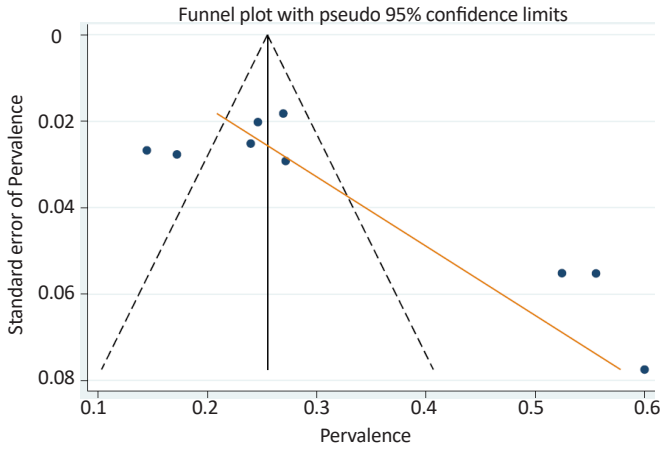

Figure 1. Publication bias for the prevalence of mortality among VLBW neonates

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Pooled prevalence of mortality among VLBW newborns was heterogeneous based on Asian or African countries (Asian countries=23% [95%CI:19-27] vs. African countries=55% [95%CI:48.0-27.0]; I^2=92.07%, P=0.00).

Pooled prevalence of VLBW newborns mortality in studies with sample sizes smaller than 200 subjects was lower than those of the studies with sample sizes larger than 201 subjects (26%; 95%CI:15.0-37.0 vs. 36.0%; 95%CI:27.0-45.0) (I2=92.07%, P=0.00). In logistic regression analysis, pooled odds ratio of mortality among VLBW newborns was 2.41 (95%CI: 1.887-3.069) ($P_{heterogeneity}$=0.15).

The pooled mean Apgar scores (95%CI) at the first and fifth minutes were 4.67 (95%CI:1.91-7.42, $P_{heterogeneity}$=0.815) and 7.40 (95%CI: 5.38-9.42, $P_{heterogeneity}$=0.987), respectively. The meta-analysis of prevalence of VLBW newborns receiving surfactant was 62% (95%CI:52-72), mechanical ventilation=56% (95%CI:51.0-61.0), and CPAP=41.0% (95%CI:36-46) (16-18, 20). Also, the meta-analysis of prevalence of VP newborns receiving surfactant was 32% (95%CI:29.0-36.0) and CPAP=45.0% (95%CI:41.0-49.0) (21, 22).

In the current study, prevalence of various comorbidities with VLBW or VP in neonates was also analyzed. Table 3 summarizes the results (15, 16, 18, 20-26). The most prevalent comorbidity in VLBW newborns allocated to sepsis (49.0%; 95%CI: 38.0-59.0) (15) and the least belonged to PVL (3.0%; 95%CI:2.0-5.0) (16, 18, 20). In VP group, the most prevalent and the least comorbidities were NDD (73.0%, 95%CI:57.0-0.85) and NEC (0.0), respectively (21, 22).

Summary of odds ratio of comorbidity in VLBW neonates are presented in Table 4 (10, 27-32). The univariate and multiple-regression analysis were not possible in VP newborns because of the studies limitations.

7. Discussion

The average global rate of neonatal mortality was 32 deaths per 1000 live births in 2015 (33) and about

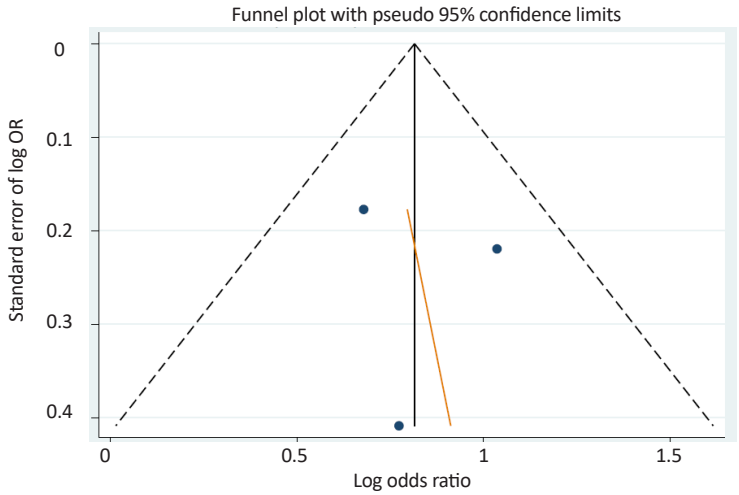

Figure 2. Publication bias for the odds ratio of mortality among VLBW neonates

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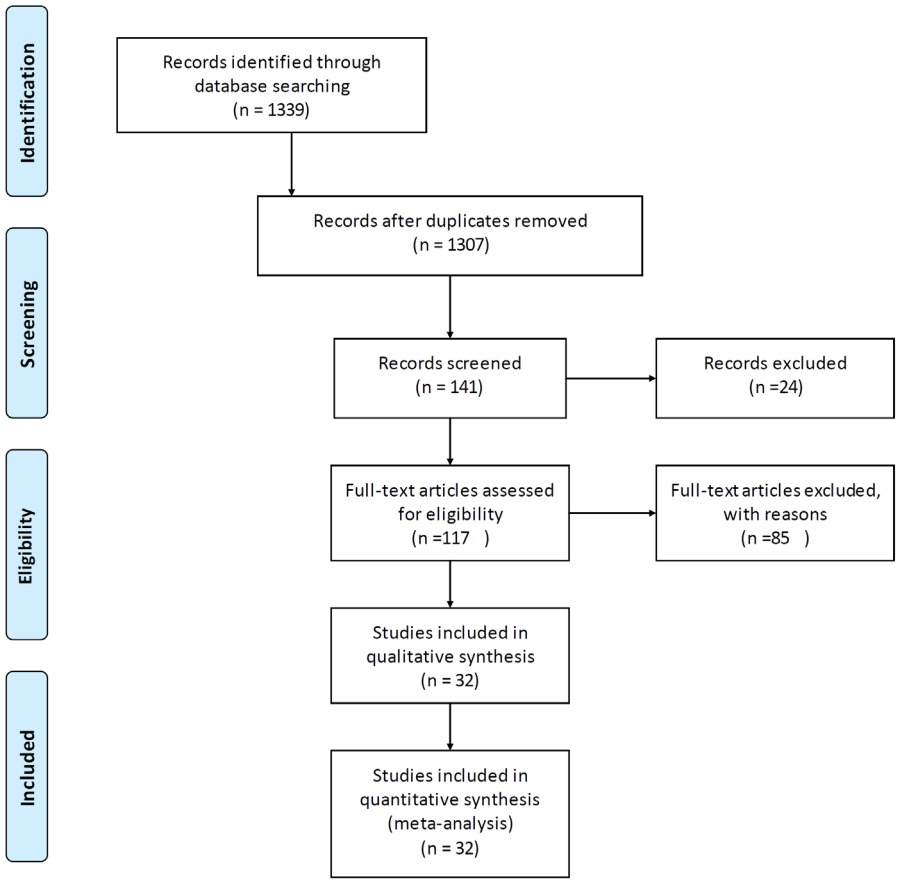

Figure 3. Flowchart of the included studies

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two-thirds of neonatal deaths occur in the African and Southeast Asian regions, according to WHO (34).

The risk of death in LBW infants is 40 times greater than normal weight babies. In addition, short gestation and preterm birth are of the main reasons of LBW (35).

The global rate of preterm birth is about 11% (from 5% in some European regions to 18% in some African regions) (35), which is responsible for 22% of neonatal mortality rate in EMR (34). Prevalence of LBW in EMR countries is high (19.5%), and accounts for 60% to 80% of all neonatal deaths either directly or indirectly (34).

Table 1. Characteristics of selected studies conducted on mortality rate of VLBW/VP newborns in Eastern Meditation region

Author(s) (Published Year)	Location	Sample Size	Type of Study
Chedid, et al. (2008) (16)	United Arab Emirates	173	Retrospective cohort
Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
Hussein, et al. (2014) (17)	Iraq	150	Retrospective cohort
Dawodu, et al. (2005) (14)	United Arab Emirates	40408	Cross-sectional
Malek-mellouli, et al. (2013) (15)	Tunis	82	Retrospective cohort
Ziadeh, et al. (2000) (11)	Jordan	386	Cross-sectional
Fakhr, et al. (2005) (12)	Egypt	480	Cross-sectional
Al Azzawi (2011) (19)	Iraq	924	Cross-sectional
Obaid, et al. (2010) (13)	Iraq	600	Retrospective cohort

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Table 2. Characteristics of the selected studies conducted on VLBW/VP newborns in Eastern Meditation region

Morbidity	Author(s) (Published Year)	Location	Sample Size	Type of Study
NEC	Chedid, et al. (2008) (16)	United Arab Emirates	173	Retrospective cohort
	Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
	Al-Abdi, et al. (2011) (20)	Saudi Arabia	18123	Retrospective cohort
ROP	Chedid, et al. (2008) (16)	United Arab Emirates	173	Retrospective cohort
	Wani, et al. (2014)	Kuwait	207	Retrospective study
BPD	Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
	Al-Abdi, et al. (2011) (20)	Saudi Arabia		Retrospective cohort
Pneumothorax	Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
	Al-Abdi, et al. (2011) (20)	Saudi Arabia	18123	Retrospective cohort
PVL	Chedid, et al. (2008) (16)	United Arab Emirates	173	Retrospective cohort
	Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
	Al-Abdi, et al. (2011) (20)	Saudi Arabia	18123	Retrospective cohort
PDA	Al Hazzani, et al. (2011) (18)	Saudi Arabia	186	Retrospective cohort
NDD	Khan, et al. (2012) (21)	Pakistan	110	Prospective cohort
	Mansouri (2001)	Saudi Arabia	92	Retrospective cohort

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NEC: Necrotizing Enterocolitis; IVH: Intraventricular Hemorrhage; ROP: Retinopathy of Prematurity; BPD: Bronchopulmonary Dysplasia; PVI: Periventricular Leukomalacia; PDA: Patent Ductus Arteriosus; and NDD: Neurodevelopmental Delay

The current meta-analysis study evaluated mortality and morbidity as well as odds ratio on VLBW /VP infants in EMR countries. The present study was the first meta-analysis in this regard. Although most studies had reported mortality (19 studies) or survival (6 studies) rate in their studied populations, different patient categorizations restricted the authors to include all the extracted literature in the present meta-analysis. Thus,

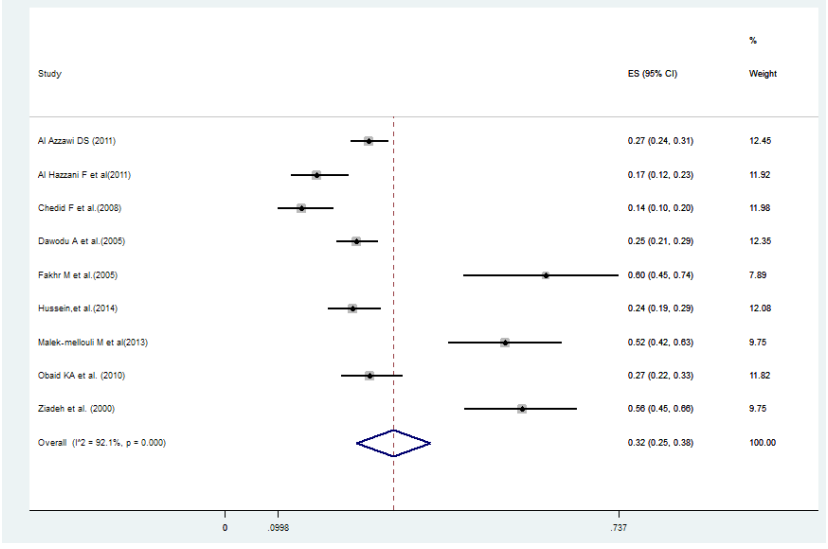

Figure 4. Meta-analysis of prevalence of mortality among VLBW newborns

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Table 3. Meta-analysis of prevalence of various disorders among VLBW and VP newborns in Eastern Meditation region

Variable	VLBW Newborn				Very Preterm Newborn			
	Number of Studies (Reference)	Meta-analysis of Prevalence (%)	95%CI	I^2 % (P)	Number of Study (Reference)	Meta-analysis of Prevalence (%)	95%CI	I^2 % (P)
NEC	3 (16-18, 20)	7.0	5.0, 9.0	0.0(0.77)	1 (22)	0.0	2.0, 4.0	-
IVH	3 (16–18, 20)	19.0	10.0, 28.0	88.8(0.00)	1 (22)	1.0	1.0, 3.0	-
ROP	2 (16, 23)	14.0	10.0, 17.0	0.0(0)	3 (22, 24, 43)	17.0	2.0, 32.0	0.89(0. 00)
BPD	2 (18, 20)	15.0	12.0, 19.0	0.0(0)	-	-	-	-
PT	2 (18, 20)	8.0	5.0, 10.0	0.0(0)	-	-	-	-
PVL	3 (16, 18, 20)	3.0	2.0, 5.0	0.0(0.55)	1 (22)	1.0	0.0, 1.0	-
PDA	1 (18)	31.0	25.0, 36.0	-	1 (22)	3.0	2.0, 5.0	-
NDD	2 (21, 26)	7.0	4.0,10.0	0.0(0)	1 (21)	73.00	57.0, 85.0	-
Sepsis	1 (15)	49.0	38.0, 59.0	-	--	-	-	-

NEC: Necrotizing Enterocolitis; IVH: Intraventricular Hemorrhage; ROP: Retinopathy of Prematurity; BPD: Bronchopulmonary Dysplasia; PT: Pneumothorax; PVI: Periventricular Ieukomalacia; PDA: Patent Ductus Arteriosus; and NDD: Neurodevelopmental Delay

Table 4. Pooled odds ratio of comorbidity in VLBW neonates

Variable	Number of Studies (Reference)	Pooled Odds Ratio	95%CI	X^2 (P)
CM	3 (24, 28, 29)	0.11	0.07-0.17	28.88(0.000)
Asphyxia	2 (30, 31)	1.10	0.75-1.60	2.92(0.232)
Sepsis	3 (30-32)	1.73	1.19-2.51	155.65(0.000)
NDD	1 (10)	0.03	0.00-0.66	0.000(.)

CM: Congenital Malformation; NDD: Neurodevelopmental Delay

only 9 studies entered into meta-analysis of prevalence of mortality in VLBW neonates.

In the current study, the pooled prevalence of mortality in VLBW was 32% (95%CI:27.0-38.0). According to a study conducted by the National Institute of Child Health and Human Development (NICHD) on 9575 VLBW and VP infants, from 2003 to 2007, the overall mortality rate was 28%, and the highest mortality rate occurred in the first 12 hours of life (36). Overall, in-hospital mortality rate among VLBW infants in the developed countries was 5% in New Zealand (2009) (37), 6.5% in Korea (2009) (38), and 12.9% in the United States of America (from 2007 to 2008) (39).

In the current review study, the pooled odds ratio of mortality in VLBW infant was 2.41 (95%CI:1.887-3.069); the finding was not heterogeneous. Due to lack of consistent studies, multiple analyses were not possible in the current review. In the NICHD study, the adjusted risk of early death was significantly high for infants born at 22nd to 24th weeks of gestation compared with the ones born at the 28th week (36). In the current study, meta-analysis of prevalence of mortality in the studied countries showed heterogeneity of mortality between African and Asian countries (55% vs. 23%).

An estimated by WHO in 2013, about 6.3 million children under five years died globally, of which 2.9 million were in African regions. About one-quarter of these deaths occur in the first month of life, and over two-thirds in the first seven days (40). According to WHO EMRO reports, 99% of infant deaths occur in the low- and middle-income countries (34) such as Southeast Asian and Sub-Saharan African countries (41).

Pooled mortality prevalence of VLBW infants in the studies performed before 2006 was higher than those of conducted after 2006 (46% vs. 26%). However, the difference was non-significant. There was a significant progress in child survival in the Western Pacific region. The overall estimations indicated that the mortality rate reduced by 65% from 1990 to 2011 (34). Because of the small number of studies, two of the subgroups could not be analyzed simultaneously (year of study and country).

Prevalence of mortality was different based on the sample size (under 200 cases, 26% and above 201 cases, 36%), and other factors probably had synergistic effects on this heterogeneity too. However, there was not enough information to estimate these effects. The second objective of the current systematic review was to analyze comorbidities with VLBW and VP infants. Birth weight and gestational age are two of the most important factors that predict the quality of life of neonates (41). According to the included studies, there was a wide variation in comorbidities among study results. Even the same comorbidities were defined in different ways which made the analysis difficult. However, comorbidities were categorized according to the most prevalent definition in the included studies.

The rarest comorbidity in VLBW belonged to PVL (3.0%) (16, 18, 20) and the most prevalent comorbidity was sepsis (49.0%) (15). Also, meta-analysis of regression analysis showed a significant comorbidity between VLBW and sepsis (OR=1.73) (28-30). In the VP group, the most common and the rarest comorbidity were NDD (73.0%) and NEC (0.0) (21, 22).

In the NICHD study, Respiratory Distress Syndrome (RDS) was the most common disease among VLBW infants and other comorbidities were as follows: 36% late-onset sepsis, 16% severe intraventricular hemorrhage, and 11% necrotizing enterocolitis (36). Consistent with the current study, sepsis in less than 1000 g neonates was the most frequent morbidity in Ataly study (42). In the current study, BPD was reported 15.0%. However, there was only one case in Ataly study (42). In the current study, significant differences were observed between birth weight and Apgar scores at 1 minute and 5 minutes, as well as application of nasal CPAP, ventilatory therapy, and the need for surfactant therapy.

The most restrictive factor of the current study was the limitation in the eligible studies and insufficient sample sizes. For example, mortality pooled prevalence, and univariate and multiple regression analysis in VP newborns could not be estimated. Lack of information from some of EMR countries was another important limitation. Wide discrepancy in the study design, populations, mortality indicators, and neonatal definitions of morbidities created difficulty to make a perfect picture of prematurity and low birth weight and their subgroups of these regions.

8. Conclusions

In conclusion, there was a relatively huge discrepancy between the prevalence of mortality among VLBW newborns in the Asian and African countries. It seems that these statistics in EMR should be reported and evaluated independently in Asian and African countries. Septicemia caused a large proportion of deaths in VLBW newborns, therefore, it is clear that the greater proportion of neonatal mortality (caused by infections) is preventable by simple interventions and vice versa; negligence in treatment has serious consequences.

Ethical Considerations

Compliance with ethical guidelines

Ethical code number of this study is: No. 27833.

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Authors contributions

The authors contributions is as follows: Conceptualization: Fatemeh Nayeri, Mamak Shariat, Setareh Sagheb; Methodology: Leyla Sahebi, Mamak Shariat, Fatemeh Nayeri; Software: Leyla Sahebi, Zahra Emami; Validation: Fatemeh Nayeri, Setareh Sagheb, Mamak Shariat, Leyla Sahebi; Formal Analysis: Leyla Sahebi; Investigation: All authors; Resources: Leyla Sahebi, Zahra Emami, Yasamin Mohammadzadeh; Data curation: Leyla Sahebi, Zahra Emami, Yasamin Mohammadzadeh; Writing–original draft preparation: Leyla Sahebi; Writing-review & editing: Fatemeh Nayeri, Mamak Shariat, Leyla Sahebi; Visualization: Fatemeh Nayeri, Mamak Shariat, Setareh Sagheb; Supervision: Fatemeh Nayeri, Mamak Shariat; and Project administration: Fatemeh Nayeri.

Conflict of interest

The authors declare no conflict of interest.

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