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Review Article

Mortality in Neonatal Intensive Care Units in Iran: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Neonatal mortality rate is an important health index. The present study was conducted to determine the mortality rate and its causes in neonatal intensive care units (NICUs) in Iran.

Methods: Online search was done without time limit until June 2018 in several databases, such as PubMed, Web of Science (ISI), Scopus, Magiran, Barakat Knowledge Network System, SID, Iranian National Library, Regional Information Center for Science and Technology (RICST), Google Scholar search engine, and Iranian journals. The articles were qualitatively assessed after evaluating the inclusion and exclusion criteria. The Cochran's Q test and I^2 index were used to determine the heterogeneity between studies. Meta-analysis was done based on a random effects model using Comprehensive Meta-Analysis Software (version 2).

Results: Thirty-one eligible studies were analyzed. The mortality rate in 24,995 neonates admitted to NICUs in Iran was estimated to be 11.40% (95% CI: 9.10-14.20). The lowest mortality rate reported as 7.70% (95% CI: 6.01-9.82) was related to the Center of Iran, and the highest mortality rate was reported as 19.26% (95% CI: 15.82-23.24) in the west of Iran. In this regard, the difference was statistically significant (P<0.001). The most common causes of mortality in NICUs in Iran were prematurity (44.14% [95% CI: 31.95-57.08]), respiratory distress syndrome (RDS) (31.93% [95% CI: 22.83-42.66]), congenital malformation (16.09% [95% CI: 12.85-19.95]), septicemia (12.66% [95% CI: 8.87-17.75]), and asphyxia (7.58% [95% CI: 4.63-12.19]).

Conclusion: The most common causes of mortality in Iranian neonates were prematurity, RDS, and congenital anomalies. We also found the mortality rate to be acceptable (11.4%). To reduce the mortality rate, we recommend performing prenatal screening tests and genetic counseling. In addition, maternal care during pregnancy should be improved to reduce premature delivery.

Keywords: Intensive care unit, Iran, Meta-analysis, Mortality, Neonatal

Introduction

Children's health should be considered as one of the first and most important tasks of any nation, and one of the main plans of any government. Currently, the countries of the world are not ranked based on the upward trend per capita but according to decline in their child mortality (1). Extrauterine occurs right after intrauterine life. The neonatal period is referred to the first 28 days of life, which is the stage of developing physiological adaptations for extrauterine life. This period is a period of vulnerability, and the high neonatal mortality rates are due to the high level of vulnerability in this period (2).

Neonatal mortality rate is an important health index that reflects the health, nutrition, and healthcare system of a community. The neonatal causes of motility are generally divided into two categories, including biological and non-biological factors. Although biological factors, such as prematurity, infection, and asphyxia at birth, are the famous causes, non-biological causes are equally important, which include the socioeconomic status, gender, and mother's level of education (3).

According to the World Health Organization, out of 130 million births per year that occur in the

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world, about four million neonates die during the first 28 days of life. Moreover, three-fourths of these deaths occur during the first week of birth, and more than one-fourth occurs during the first 24 h of birth (4). These deaths account for more than 40% of the total mortality rate of children under the age of 5 years (5, 6).

The neonatal intensive care unit (NICU) is a tertiary health care unit that provides specialized medical care for neonates, which is why the level of mortality in this section seems to be higher than other sections of medical care (7). On the other hand, the first step in reducing the mortality rate and improving the level of this index is to identify the causes of mortality (8). Therefore, identifying the major causes of neonatal death will provide the basis for proper planning to improve care systems for pregnancy, delivery, and children.

Considering the numerous studies conducted on mortality and its causes in NICUs in Iran, conducting a systematic review and meta-analysis seems necessary. A meta-analysis includes the use of specific statistical methods to summarize the results of different studies to find the most accurate form of relationship between the variables under study. These statistical methods help collect the data of various articles and summarize them, and personal opinions have no effect on this process (9-11). This study aimed to determine the mortality rate and its causes in NICUs in Iran.

Methods

Study protocol

This review article was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guideline (11). Two authors independently took all the steps. In case of disagreement between the two authors, a third author was involved.

Search strategy

To identify relevant studies, a comprehensive search was done in national and international databases, including PubMed, Web of Science (ISI), Scopus, Magiran, Barakat Knowledge Network System, SID (Scientific Information Database), Regional Information Center for Science and Technology (RICST), Iranian National Library, Google Scholar search engine, and Iranian journals. The MeSH (medical subject headings) terms were combined using Boolean operators 'OR' and 'AND'. The keywords used here were "Infant, Newborn"[MeSH], "Intensive Care Units, "Neonatal"[MeSH], "Mortality"[MeSH], "Causality" [MeSH], "Etiology" [Subheading], "Neonatal"[Text Word], and "Iran"[MeSH]. Advance search in the PubMed database is shown in Appendix 1. Online search was done without a time limit until June 2018. All references were reviewed in the selected articles to find more publications.

Inclusion and exclusion criteria

Only the studies that investigated the neonatal mortality in Iran were included. Published studies were selected in both Persian and English. The exclusion criteria were 1) duplicates, 2) non-relevant studies, 3) non-random sample size, 4) studies in other sections (other than NICU), and 5) studies on specific neonatal groups, such as preterm neonates, low birth weight (LBW) neonates, 6) population other than neonates (0-28 days), 7) non-Iranian studies, and 8) review articles, case reports, and letters to editor without quantitative data.

Study selection

First, all the related articles with an affiliation that included Iranian authors were collected, and after completing the search and exclusion of duplicates, two researchers reviewed the title and abstract independently. If there was any doubt about the worthiness of the article based on the abstract, the full text was studied, and if the full text was not available, we would contact the author.

Qualitative assessment

To assess the quality of the identified literature, the modified Newcastle Ottawa Scale for cross-sectional studies was used. This scale includes eight sections in four categories (12). The minimum and maximum scores on this checklist were 0 and 9, respectively. Accordingly, the studies were divided into three categories, including 1) low quality with a score below 5, 2) moderate quality with a score of 5-6, and 3) high quality with a score of 7-8. Finally, studies that achieved the minimum score (5) were selected for the meta-analysis.

Data Extraction

The data were extracted by a checklist that included the name of the first author, journal's name, year of publication, year of study, location, study design, number of neonates admitted to NICUs, number of deaths, number of deaths based on gender, causes of mortality, and other information.

Data analysis

Meta-analysis was performed using Comprehensive Meta-Analysis Software (version 2). The data were combined using a random effects model. Binomial distribution was used to estimate the standard error. Results were reported based on the total prevalence, as well as subgroups, with a 95% confidence interval (CI). The Cochran's Q test and I^2 index were used to determine the heterogeneity between studies. The Cochran's Q test was used to assess whether the variation of tests was consistent with chance, and P-value less than 0.1 was significant for heterogeneity (13).

Considering the statistical heterogeneity between the studies, the I^2 index was used as a quantitative index instead of the chance index to estimate the variance ratio between studies (I^2<25% indicates low heterogeneity, 25-49% indicates average heterogeneity, 50-74% indicates considerable heterogeneity, and 75-100% indicates high heterogeneity) (14). To assess the possible heterogeneity in mortality rates, meta-regression was performed based on the year of study, and subgroup analysis was performed based on geographical regions. Sensitivity analysis, in which one study is removed at a time, was performed to verify the stability and reliability of the data. Begg and Egger's tests were used to assess the publication bias of studies, and P-value less than 0.05 was considered significant.

Results

Overview of Search

In the initial search, 320 studies were found to be related to neonatal mortality in Iran. After reviewing the full text of 78 relevant studies, 48 studies were excluded due to lack of necessary criteria. Finally, 31 eligible studies (27 studies for neonatal mortality and 14 studies for the causes of mortality) entered qualitative assessment stage (Figure 1). Table 1 shows the characteristics of each study.

Mortality rate in all studies

Total heterogeneity was very high in the studies (I^2=97.39, P<0.001). The mortality rate among 24,995 neonates admitted to NICUs in Iran was estimated to be 11.40% (95% CI: 9.10-14.20).

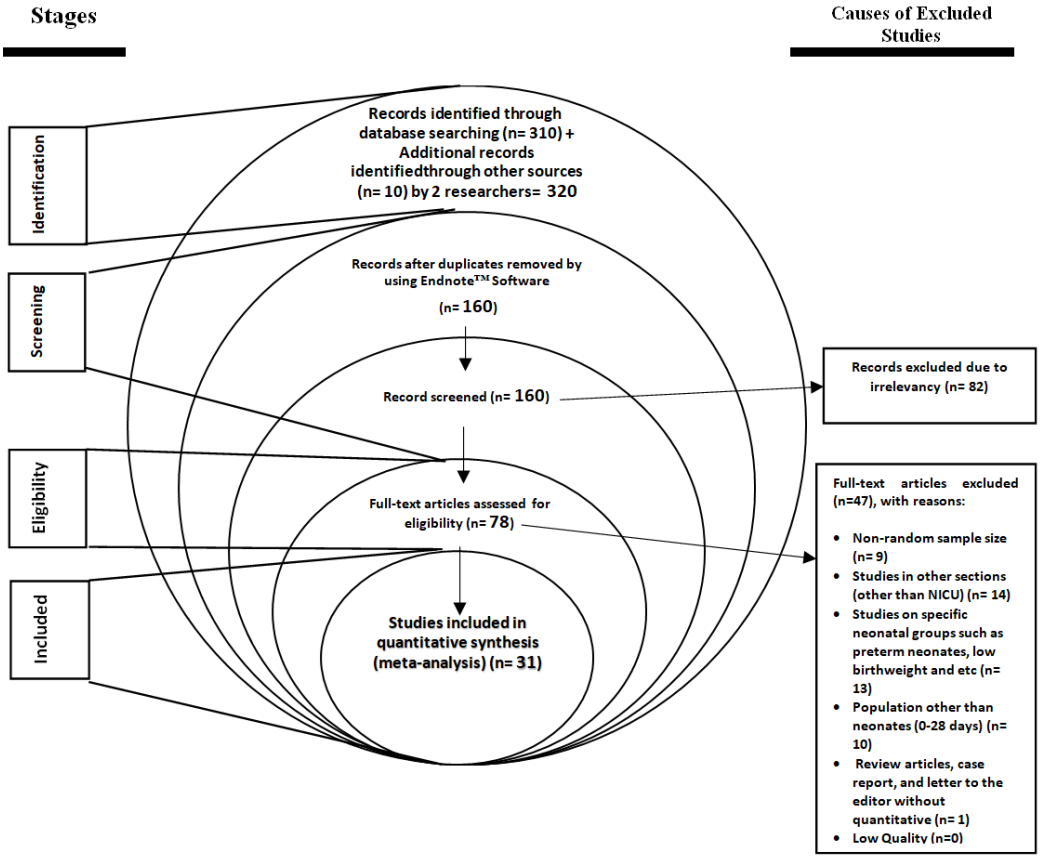


Figure 1. PRISMA Flow Diagram

Table 1. Summary of characteristics in studies in meta-analysis

Reference	First author, published year	Year	Study design	Region	Place	Sample size		Most common cause of death	Quality
						Admitted (n[a])	Death (n)		
15, 16	Javanmardi, Z. 2008 and 2010	2005	Cross-sectional	Center	Isfahan	251	NR[b]	Prematurity	Moderate
17	Zeinalzadeh, AH. 2017	2013-2014	Cross-sectional	North	Tabriz	891	68	Congenital malformation	High
18	Jaberi, Z. 2013	2003	Cross-sectional	Center	Tehran	485	56		High
18	Jaberi, Z. 2013	2005	Cross-sectional	Center	Tehran	747	53		High
18	Jaberi, Z. 2013	2006	Cross-sectional	Center	Tehran	520	49		High
18	Jaberi, Z. 2013	2004	Cross-sectional	Center	Tehran	884	44		High
18	Jaberi, Z. 2013	2007	Cross-sectional	Center	Tehran	600	40		High
18	Jaberi, Z. 2013	2002	Cross-sectional	Center	Tehran	470	36		High
18	Jaberi, Z. 2013	2008	Cross-sectional	Center	Tehran	720	34		High
18	Jaberi, Z. 2013	2009	Cross-sectional	Center	Tehran	668	32		High
18	Jaberi, Z. 2013	2010	Cross-sectional	Center	Tehran	735	31		High
18	Jaberi, Z. 2013	2001	Cross-sectional	Center	Tehran	368	25		High
19	Mirzarahimi, M. 2008	2006-2007	Cross-sectional	North	Ardebil	218	94		High
20	Safari, H. 2009	2006-2008	Cross-sectional	Center	Tehran	1017	108	RDS [c]	Moderate
21	Aramesh, M R. 2014	2011-2012	Cross-sectional	South	Ahvaz	1620	284	Prematurity	Moderate
22	Aref Nejad, M. 2016	2014	Cross-sectional	East	Zabol	NR	110	Prematurity	Moderate
23	Ziba, M. 2008	2007	Cross-sectional	Center	Kashan	700	63	Prematurity	Moderate
24	Fallahi. M. 2009	2004-2007	Cross-sectional	Center	Tehran	NR	60		High
25	Sareshtedari, M. 2009	2010	Cross-sectional	Center	Qazvin	225	50	RDS	High
26	Bala Ghafari, A. 2010	2003-2006	Cross-sectional	North	Sari	1238	222	RDS	High
27	Hoseini, BL. 2015	2006-2013	Cross-sectional	East	Sabzevar	3667	375	RDS	High
28	Mirfazeli, A. 2014	2008-2011	Cross-sectional	North	Gorgan	3195	95	RDS	High
29	Basiri, B. 2015	2012	Cross-sectional	West	Hamadan	492	134	Prematurity	High
30	Khani, S. 2008	2005-2007	Cross-sectional	North	Sari	504	119	RDS	Moderate
31	Azami M, 2018	2015-2016	Cross-sectional	South	Ahvaz	1040	123		High
32	Sabzehei MK, 2018	2015-2016	Cross-sectional	West	Hamadan	600	78		High
33	Babaei H, 2018	2014	Cross-sectional	West	Kermanshah	956	195		High
33	Babaei H, 2018	2015	Cross-sectional	West	Kermanshah	1012	188		High
33	Babaei H, 2018	2016	Cross-sectional	West	Kermanshah	978	183		High
34	Taheri F, 2007	2005-2006	Cross-sectional	East	Birjand	445	92		Moderate

a Number; b Not reported; c Respiratory distress syndrome

The lowest and highest mortality rates were in Ardabil (43.1%) (2007-2008) and Gorgan (3.0%) (2008-2011), respectively (Figure 2).

Sensitivity Analysis and Cumulative Analysis of Neonatal Mortality

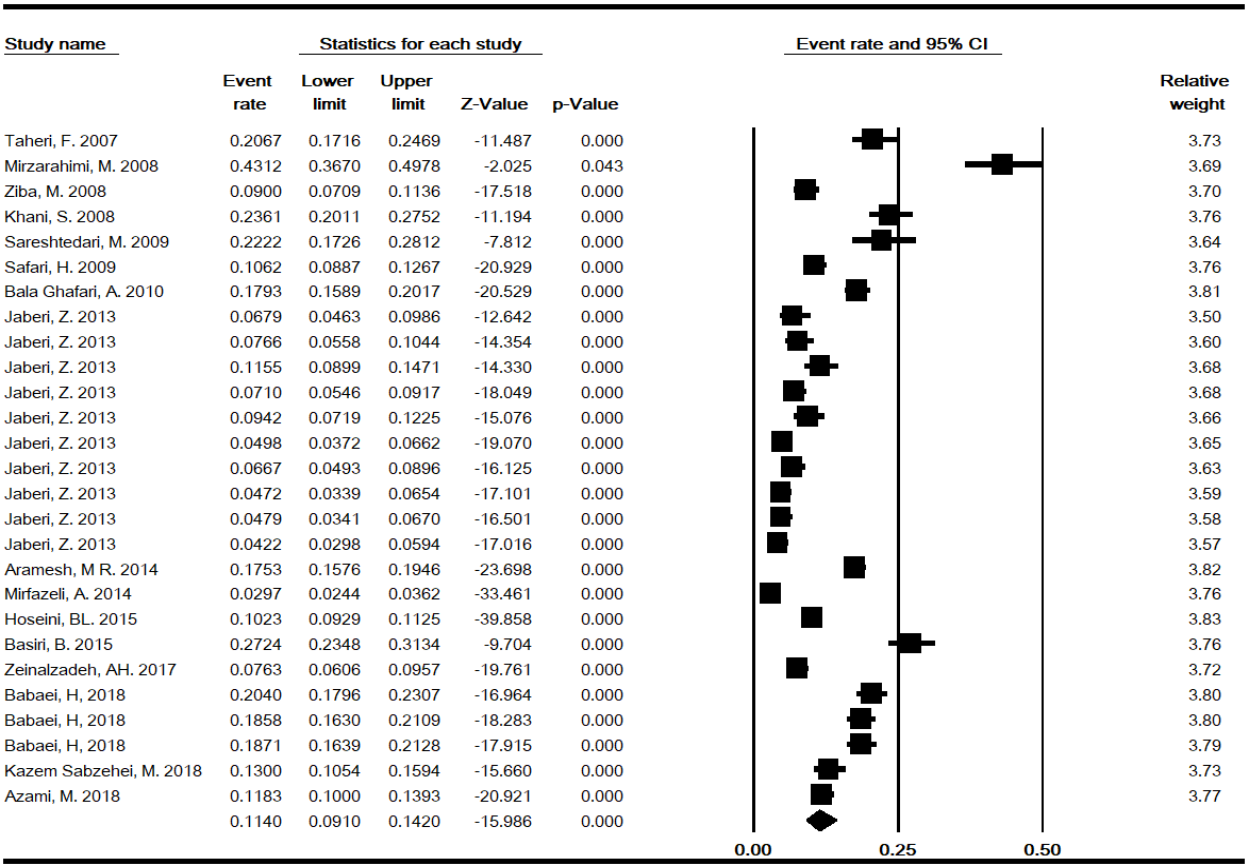
The sensitivity analysis of neonatal mortality rates in NICUs in Iran was estimated irrespective of a study at a time, and the results in Figure 3-A show that the overall result is robust. Cumulative mortality analysis based on the year of publication is shown in Figure 3-B.

Meta-regression

The meta-regression model for the relationship between the mortality rate in NICUs and the year of the study showed that the mortality rate was not significant (P=0.193) (Figure 4).

Subgroup Analysis

Overall, 13, 2, 5, 5, and 2 studies were related to the Center, South, North, West, and East of Iran, respectively. The mortality rate in NICUs is shown in Table 2. The lowest mortality rate was related to the Center of Iran (7.70% [95% CI: 6.01-9.82]), and the highest mortality rate was reported in the West of Iran (19.26% [95% CI: 15.82-23.24]). In this regard, the difference was significant (P<0.001). The subgroup analysis of mortality in NICUs based on the quality of studies showed no statistically significant difference (P=0.081) (Table 2). The mortality rates in NICUs during the



Meta Analysis

Figure 2. Mortality rate in neonatal intensive care units in Iran; random effects model; * assessment of mortality rates in studies by Jabari Z. et al. and Babaei H. et al. during several years

Table 2. Mortality in neonatal intensive care unit (NICU) based on region and quality of studies and most common causes of mortality in NICUs in Iran

Variable		Studies (n[a])	Sample (n)		Heterogeneity		95% CI[b]	Prevalence (%)	Meta-regression		Bias test	
			All	Event	I^2	P-Value			Trend	P-value	Egger's	Begg's
Region	Center	13	8139	621	97.66	< 0.001	6.01-9.82	7.70	-	-	-	-
	East	2	4112	467	97.56	< 0.001	7.07-27.81	14.62	-	-	-	-
	North	5	6046	598	99.14	< 0.001	5.82-31.03	14.29	-	-	-	-
	South	2	2660	407	93.63	< 0.001	9.76-21.05	14.51	-	-	-	-
	West	5	4038	778	90.11	< 0.001	15.82-23.24	19.26	-	-	-	-
	Test for subgroup differences: Q=33.67, df (Q)=4, P<0.001								-	-	-	-
Year of studies	2001-2005	6	2942	192	86.38	<0.001	4.56-9.67	6.67	-	-	-	-
	2006-2010	13	6364	734	97.26	<0.001	7.74-18.17	12.01	-	-	-	-
	2011-2016	8	8100	692	94.40	<0.001	12.89-20.02	16.14	-	-	-	-
	Test for subgroup differences: Q=17.11, df (Q)=3, P=0.001											
Quality	High	22	20709	2205	97.61	< 0.001	8.07-13.80	10.60	-	-	-	-
	Moderate	5	4286	666	94.82	< 0.001	9.85-20.96	14.35	-	-	-	-
	Test for subgroup differences: Q=3.040, df (Q)=1, P=0.081								-	-	-	-
Most common causes of mortality	Prematurity	7	1008	486	93.18	<0.001	31.95-57.08	44.14	Asc[c]	0.332	0.293	0.229
	Congenital malformation	13	2300	356	78.19	<0.001	12.85-19.95	16.09	Asc	0.815	0.432	0.669
	Respiratory distress syndrome	11	2035	691	94.85	<0.001	22.83-42.66	31.93	Asc	0.742	0.497	0.436
	Septicemia	11	1921	276	86.22	<0.001	8.87-17.75	12.66	Asc	0.950	0.441	0.086
	Pneumonia	4	979	31	83.41	<0.001	1.82-10.04	4.35	Des	0.479	0.71	-
	Asphyxia	10	1963	141	87.27	<0.001	4.63-12.19	7.58	Asc	0.457	0.446	0.591
	Disseminated intravascular coagulation	2	301	13	90.58	<0.001	3.50-10.15	6.01	-	-	-	-
	Metabolic disease	4	1252	26	14.31	0.321	1.45-3.36	2.21	Des[d]	0.705	0.734	0.601
	Meconium aspiration syndrome	4	1127	15	0	0.581	0.86-2.34	1.42	Des	0.187	0.734	0.393
	Intraventricular hemorrhage	2	689	13	94.35	<0.001	0.14-26.06	0.22	-	-	-	-

[a] Number, [b] Confidence interval' [c] Ascending, [d] Descending

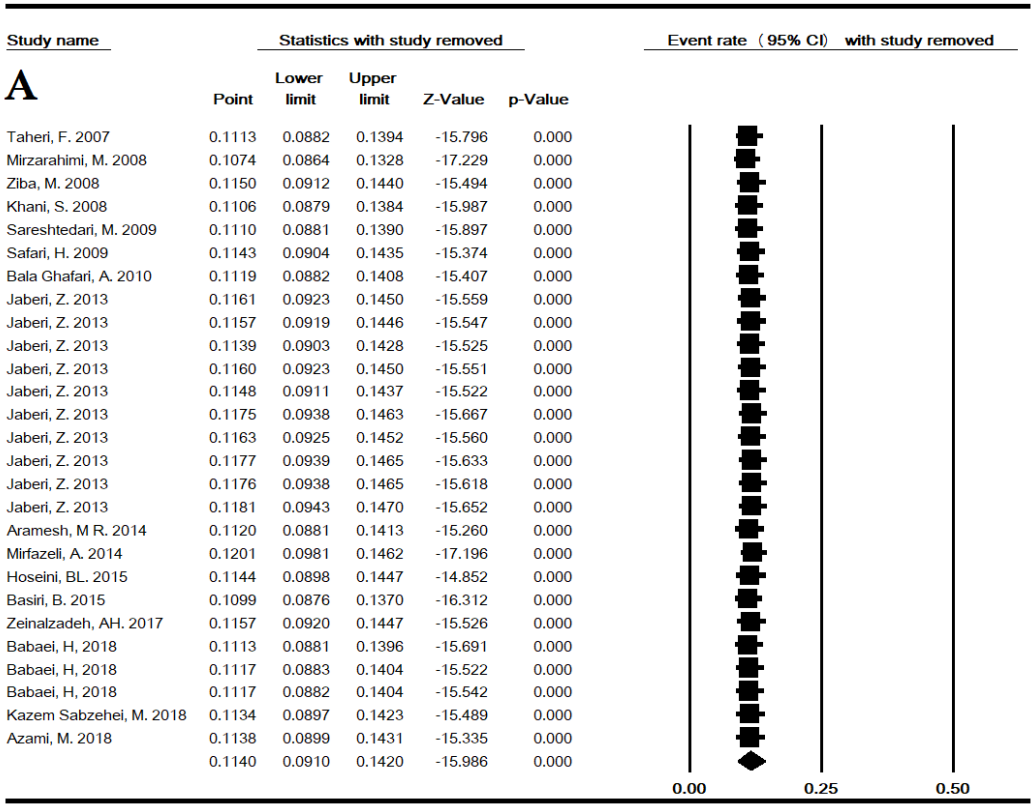


Figure 3. Sensitivity analysis (A) and cumulative analysis (B) of mortality rate in neonatal intensive care units in Iran

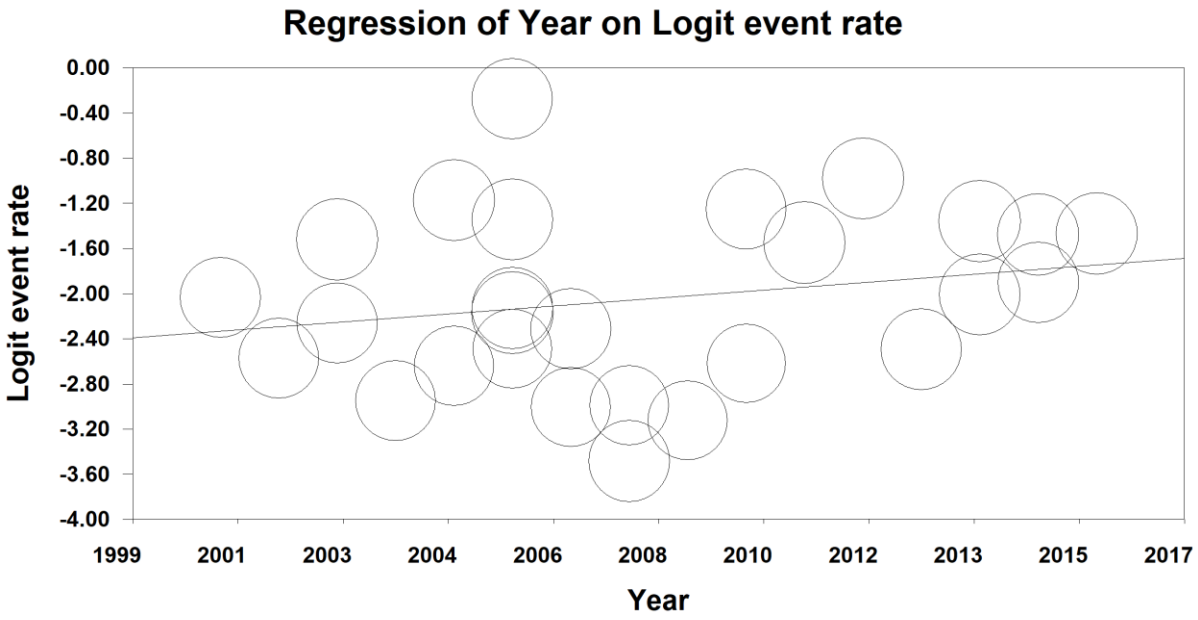


Figure 4. Relationship between mortality rate in neonatal intensive care units in Iran and year of study

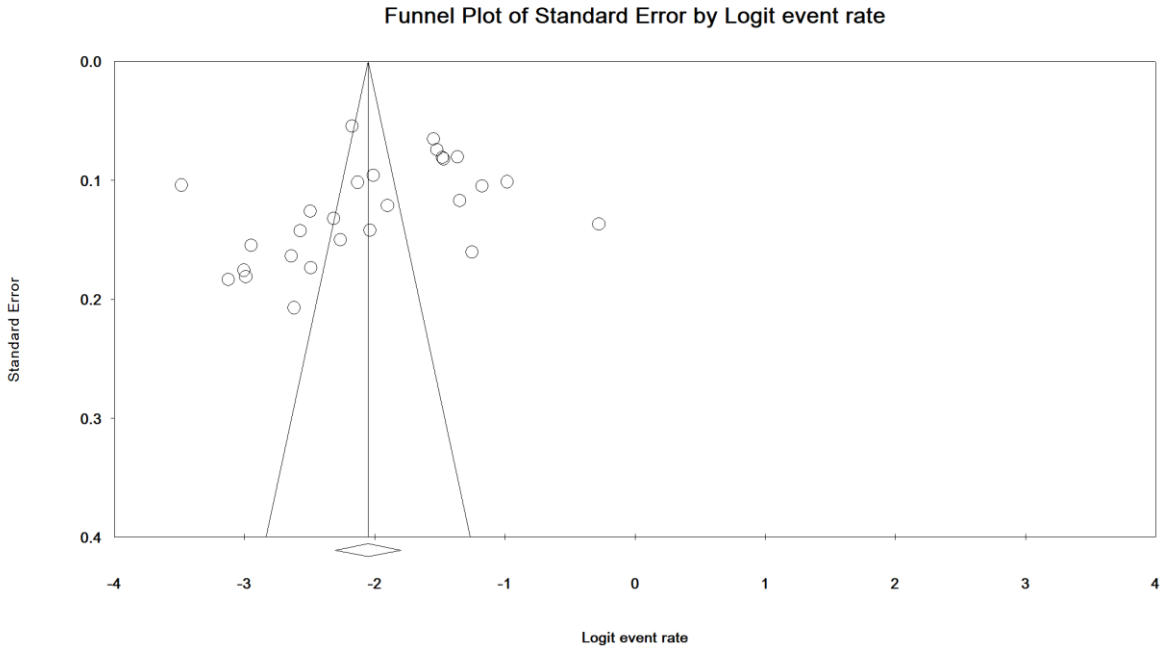


Figure 5. Publication bias of mortality rate in neonatal intensive care units in Iran

years 2001-2005, 2006-2010, and 2011-2016 were estimated to be 6.67%, 12.01%, and 16.14%, respectively (Table 2).

Causes of Mortality

The most common causes of mortality in NICUs were prematurity (44.14% [95% CI: 31.95-57.08]), respiratory distress syndrome (RDS) (31.93% [95% CI: 22.83-42.66]), congenital malformation (16.09% [95% CI: 12.85-19.95]), septicemia (12.66% [95% CI: 8.87-17.75]), and asphyxia (7.58% [95% CI: 4.63-12.19]) (Table 2).

Publication bias

The publication bias of the studies conducted on mortality rate in NICUs in Iran was shown in the form of a funnel plot, and the P-values for Begg's and Egger's tests were 0.059 and

0.083, respectively. In addition, the hypothesis of publication bias was rejected (Figure 5).

Discussion

The present study was the first meta-analysis performed on the mortality rate and its common causes in NICUs in Iran. This study was unique because it included the neonates of all birth weights. In this study, the mortality rate among 24,995 neonates in NICUs in Iran was estimated to be 11.4% based on a random effects model.

Studies that report the results of all neonates admitted to NICUs and include all deaths in the hospital have reported the lowest mortality rate (35-41). The neonatal mortality rates in the NICU reported in different countries were 0.2% in Israel (35), 4-7.6% in Canada (36-37), 7.9% in Australia (38), 8.9% in Portugal (39), 22.4% in Saudi Arabia (40), and 29.1% in Egypt (41). This rate is reported to be 0.2% to 29% worldwide (35-47). The mortality rate in other studies includes LBW neonates (8-44%) (48-50), extremely preterm neonates (8-18.8%) (51-52), premature neonates (20.6%) (53), and very LBW neonates (34.6%) (54-57).

In a review article, the overall mortality rate in NICU in developed countries was 4% to 46%, and it was reported as 0.2% to 64.4% in developing countries (6). On the contrary, premature and LBW had more severe problems and a higher risk of death. However, recent studies have also emphasized on the prognostic differences between neonates born with similar weight in different NICUs (6, 58).

In addition to differences in population risk, such differences are also related to the difference in equipment, type, and severity of disease in admitted neonates, as well as the performance of physicians and neonatal nurses (59). Comparing the results of this study with global statistics, we find that Iran is in a better condition than other developing countries in this regard, but more efforts are required to reach the level of developed countries.

In the present study, the significant cause of heterogeneity between studies was the location of studies. The mortality rate in the West of Iran was significantly higher than that of the central regions, which could indicate the differences in the equipment or performance of physicians and neonatal nurses in different regions of Iran. In the present study, the most common cause of mortality in Iranian neonates was prematurity, accounting for about half of the deaths. This result is consistent with the results of several studies from other countries (36-38).

Although the mortality rate varies in different NICUs, it remains high in some developed countries (6). Prematurity is a very common etiology for neonatal deaths because most of the neonates who died in hospital (35, 37) were LBW neonates (49) or very LBW neonates (33) who were all prematurely born. This can be attributed to the high prevalence of preterm delivery. In fact, in 2005, the World Health Organization estimated that 12.9 million births of all births (9.6%) in the world were premature (60). In addition, the prevalence rate of preterm delivery in Iran was reported to be 9.2% in a review article, which is close to global statistics (61).

International organizations, such as the World Health Organization and the United Nations International Children's Emergency Fund, consider standards for effective health services in hospitals and health centers. On the other hand, the birth of a premature infant is still associated with separation from the family and admission to the NICU, which can impose a lot of stress on parents (62).

The second most common cause of mortality in the present study was RDS, which accounts for more than one-third of the cases. The findings of studies in other countries are consistent with the results of the present study (47, 55, 6). The RDS is one of the major causes of neonatal mortality worldwide. However, limited information is available regarding the RDS-specific mortality rate in low-income countries. Improving prenatal care and reducing risk factors, as well as joint use of surfactants and anabolic steroids, are likely to provide better outcomes for neonates with RDS (8).

According to the results, congenital anomaly is another common cause of mortality in Iranian neonates. These results indicate that congenital anomalies are the major causes of admission to NICU and death, and they show the importance of developing strategies to reduce the incidence of congenital anomalies and improve prenatal diagnosis, which were differently reported in other studies (63-64). Infection and asphyxia at birth (the major cause of hypoxic-ischemic encephalopathy) were also significantly related to the causes of NICU mortality. This indicates the fact that several causes of neonatal death may be preventable (36).

The publication bias in the studies of mortality rate in NICUs in Iran was not significant. However, in survey studies, bias is more likely to occur as there is an increased chance of publishing articles that have a positive result, and such studies are

more commonly observed in the search. However, publication bias was rejected in the present study, which is associated with the causes of the mortality rate.

Limitations

One of the limitations of the present study was the failure to differentiate the mortality rate according to gender in previous studies. Another limitation was the fact that some of the less frequent common causes of mortality were mentioned as "other causes" in most studies, which could not be analyzed. In addition, the present study failed to provide a statistical indication of early and delayed mortality rate due to the lack of such statistics in previous studies, which was considered as another limitation of this study.

Conclusion

The most common causes of death in the present study were prematurity (44.14%), RDS (31.93%), congenital anomalies (16.09%), and septicemia (12.66%). We also noted the rate of mortality to be acceptable (11.4%). To reduce this rate, we recommend performing prenatal screening tests and genetic counseling. In addition, maternal care during pregnancy should be improved to reduce preterm delivery. The NICUs require a sufficient number of skilled nurses and physicians, since ignoring the ratio of caregivers to patients due to financial problems may lead to major health problems.

Acknowledgments

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Conflicts of interests

There are no conflicts of interest among the authors of this study.

Financial support

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Appendix 1. PubMed combination search

1. exp "Infant, Newborn" [MeSH]
2. exp "Neonatal" [Text Word]
3. exp "Intensive Care Units, Neonatal" [MeSH]
4. exp "Mortality" [MeSH]
5. exp "Causality" [MeSH]
6. exp "Etiology" [Subheading]
7. exp "Iran" [MeSH]
8. 1 OR 2 OR 3
9. 5 OR 6
10. 4 AND 7
11. 7 AND 8
12. 7 AND 9

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