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Limit of Premature Viability—A Comparison of Several Countries: Systematic Review

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ABSTRACT

Background: The objective was to carry out a systematic analysis of mortality in preterm infants from different countries to answer the question about which countries have the highest and lowest survival rates for extremely premature newborns.

Methods: The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with which articles, drawn from sources such as PubMed, ScienceDirect and Google Scholar and published between 2016 and 2021, were analyzed. Pregnancies up to 37 weeks of gestation were considered.

Results: Out of a total of 7,908 articles with the research terms, 14 articles were included. The most extreme prematurity case occurred in Korea with a female newborn of 21 weeks of gestation. The results show that high income countries fared better than low-income countries in securing low mortality rates. These countries include Japan (4.17%), Sweden (7.65%) and Finland (7.84%). In contrast, low-income countries were less able to manage the incidence of mortality among premature babies. Another notable finding was an extreme case of prematurity which occurred in Korea with a female of 21 weeks of gestation.

Conclusion: Mexico has one of the highest mortality percentages among extreme premature newborns. Possibly, the economic development of each country determines the number of resources allocated to the care of premature neonates which determines survival rates. On the other hand, each country has different therapeutic approaches, legal and ethical frameworks, and may offer proactive therapy or counseling to parents to provide palliative care.

Key words: Economic Development, Extremely Premature, Perinatal Care, Perinatal Mortality, Technology.

1. INTRODUCTION

A periviable birth refers to a delivery that occurs between 20 0/7 weeks and 25 6/7 weeks of gestation (WG). Newborns born at 23 WG have a survival of 5 to 6%, and even among survivors, significant mortality is 98 to 100%[1]. It is important to keep in mind that, according to the World Health Organization (WHO), a newborn is premature when it born before 37 WG and is extremely preterm when if born before 28 WG[2].

The high mortality associated with prematurity, positions it as the leading cause of death in children under the age of 5. In low-income countries, more than 90% of extremely premature infants die during the first days of life. In contrast, high-income countries have less than 10% of their extremely preterm infants die[2].

The management of very premature infants consists of a series of difficult decisions about the termination of pregnancy or to perform neonatal resuscitation, giving multidisciplinary and expensive treatment or palliative care. Such steps require a multidisciplinary team along with the relatives, who sometimes must decide whether to continue or interrupt the pregnancy for the risks faced by the maternal-fetal binomial[3]. Another focus is aimed at preventing preterm delivery (Table 1)[4].

The use of corticosteroids as prenatal therapy for fetal maturation when premature delivery is suspected has been very useful in reducing neonatal morbidity and mortality in extremely premature infants. Of this group, betamethasone and dexamethasone are the most widely used therapies in

prenatal care. These should be considered for use in cases of extreme prematurity from 07/23 WG and are already recommended for 24 0/7 to 25 6/7 WG[4,5]. Some corticosteroids are useful for the prophylactic treatment of neurodevelopmental impairment, with hydrocortisone being the one that has been shown to have the fewest adverse effects[6,7].

Immediate perinatal management consists of palliative care and life-prolonging treatments. Palliative care is based on obstetric and newborn care to improve the quality of life of the latter, who may have life-limiting conditions (lethal fetal conditions, with little or no chance of survival ex-uterus), which are made known prenatally and informed consent is required to carry them out[3]. Within the treatment to prolong life, there are different alternatives used with specific objectives (Table 2)[1]. The objective was to carry out a systematic analysis of mortality in preterm infants from different countries to answer the question about which countries have the highest and lowest survival rates for extremely premature newborns.

2. MATERIALS AND METHODS

2.1 Study Design

It was performed a systematic review between January and March 2021. This study was carried out under the guidelines set by the Preferred Reporting Items for Systematic Review and MetaAnalyses (PRISMA)[8], using the following terms ((limit) AND (fetal)) AND (viability), (fetal) AND (periviability) and ((outcomes) AND (extremely)) AND (premature). PRISMA consists of a 27-item checklist and flow diagram for transparent reporting of a systematic review. It is used to record and report on the number of articles found. An especially important issue is to document decisions for excluding and including records throughout the process.

Multicenter, observational studies, case reports, research articles, and data published between 2016-2021 were included, regarding live and dead preterm infants with the lowest GA with recorded survival and populations limited to a single country. Pregnancies up to 37 weeks of gestation were considered. The search was carried out in the databases: PubMed, ScienceDirect, and Google Scholar. Of the articles returned in the search, those that were systematic reviews were discarded to avoid duplication of information. Those from which complete information (country, period of study population, number of cases, overall mortality, weight, treatment used, and conditions related to the cause of death were eliminated) could not be extracted were also discarded (Figure 1).

Table 1: Strategies to Prevent Preterm Delivery

Prevention Level	Actions
Primary Prevention	Contraception. Single embryo transfer when conception is attempted by In Vitro Fertilization. 17-α-Hydroxyprogesterone Caproate. Smoking cessation.
Secondary Prevention	Vaginal progesterone. Cervical cerclage. Tocolysis. Corticosteroids. Magnesium Sulfate for neuroprotection.

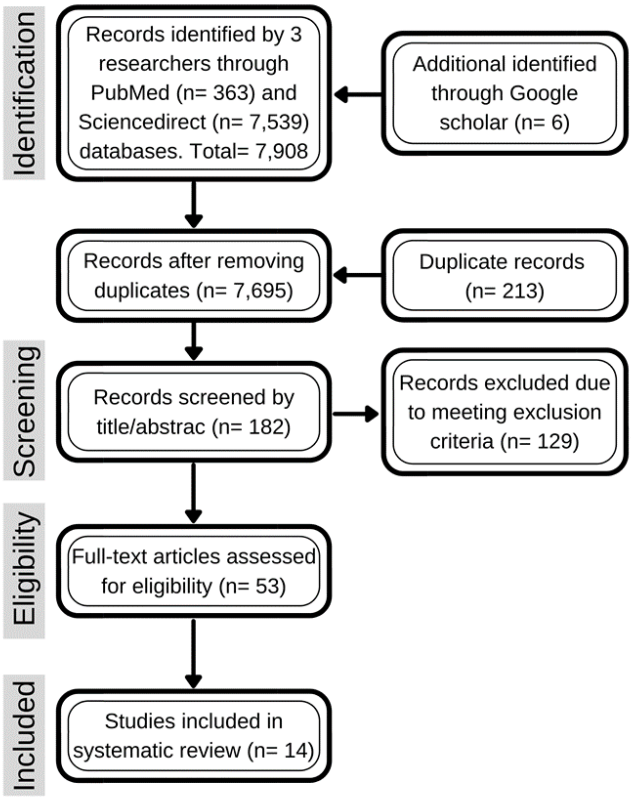

Figure 1: Process of Literature Identification and Studies Selection

Selection process

For the quality assessment of the studies included in this review, the methodology of the study cohorts and the clinical case were independently analyzed by 2 reviewers using the Joanna Briggs Institute (JBI) checklist for cohort studies and the JBI checklist for case reports. Upon completion of the review by both authors, a third author reviewed the studies and the checklists to avoid interpretations and biases by the first reviewers[9].

2.2 Data Collection

A data extraction form was developed for the information from each study; I) details of the study (country, year of publication, name of the article and type of study); II) Year of the study population; III) Number of cases; IV) Mortality; V) Age in WG; VI) Weight; VII) Therapy used and VIII) Conditions related to the cause of death.

The neonatal mortality percentage was calculated considering all the neonates mentioned in the selected articles. One limitation of this study is not having considered publications in more lan-

Table 2: Treatment Options for Premature Newborns

Palliative Care	Life-Prolonging Treatment
• **Initial Consultation**: Fetal Diagnosis, Palliative Goals, and Mother/ Family Decisions. • **Delivery Plan** : Intrapartum Fetal Monitoring and Mode of Delivery. • **Newborn Bonding**: Skin-to-Skin Contact, Warmth, Hydration, Feeding, and Breastfeeding, management of respiratory distress. • Pain control. • Emotional support to parents and family after delivery. • Bereavement counseling.	• Immediate Resuscitation. • Transferring the Woman Before Delivery. • Caesarean delivery. • Respiratory support.

guages.

The protocol was approved by the Ethics in Research Committee of the Hospital Materno-Perinatal "Mónica Pretelini Sáenz," Health Institute of the State of Mexico (ISEM), Toluca, Mexico, and informed consent was waived as the medical data was obtained from historical files. This protocol was registered in the State Health Research Registration System.

2.3 Data Availability Statement

The data supporting the findings in this study is available on Zenofo at https://zenodo.org/uploads/14740152(DOI10.5281/zenodo.14740151)

3. RESULT

A total of 14 articles met the inclusion criteria: 11 retrospective studies, 2 prospective and 1 case report. The total study population is 221,883 neonates with 21,853 deaths (9.85%), considering studies from 14 countries: Mexico (n=4), Korea (n=3), Japan (n=3), Sweden (n=3), Australia / New Zealand (n=2), Canada (n=2), Spain (n=2), France (n=2), Israel (n=2), UK (n=2), Switzerland (n=2), USA (n=1), Finland (n=1) and Italy (n=1) (Figure 2 and Table 3).

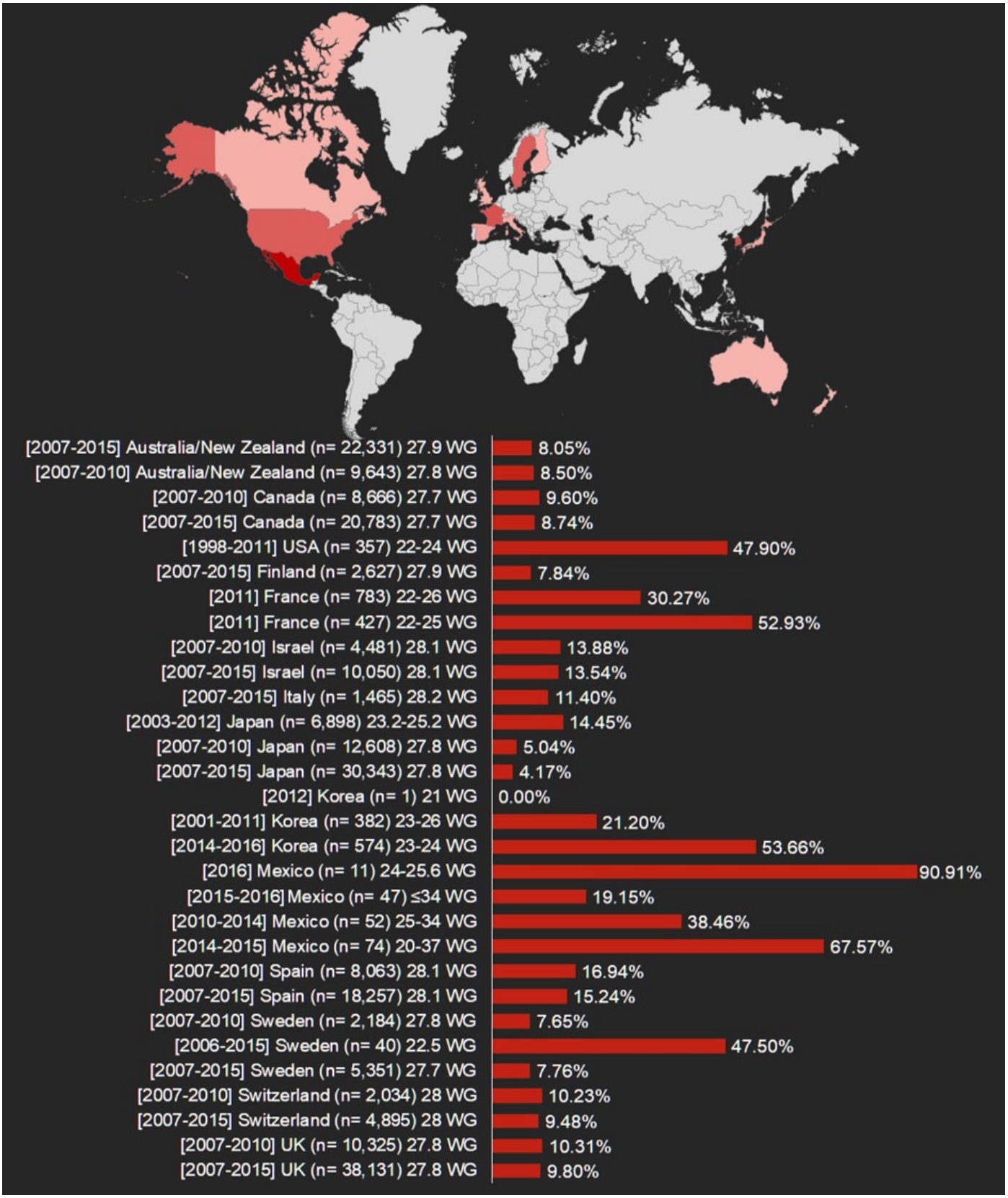

Figure 2: The Study Period, Country, Sample Size, Gestational Age in Weeks of Gestation (WG) and Mortality (%) are Shown.

Table 3: Neonatal Characteristics of Included Studies

Country, Year of Publication, Type and Period of Study	Cases (n) and Mortality (%)	WG and Weight (g)	Therapy (%)	Conditions Related to Cause of Death and Comorbidities (%)
1. Australia and New Zealand, 2019. RS (2007-2015)[10].	22,331 (8.05)	27.9 (1,064)	ANS (90.9)	BPD (28.1), SNI (6.6) and treated ROP (2.8).
2. Australia and New Zealand, 2016. RS (2007-2010)[11].	9,643 (8.50)	27.8 (1,062)	ANS (90)	BPD (24), IVH grade >3/PVL (7), IVH grade >3 (6), PVL (3) and ROP (3).
3. Canada, 2016. RS (2007-2010)[11].	8,666 (9.60)	27.7 (1,049)	ANS (84)	BPD (25), IVH grade >3/PVL (11), IVH grade >3 (10), PVL (6) and ROP (4).
4. Canada, 2019. RS (2007-2015)[10].	20,783 (8.74)	27.7 (1,050)	ANS (88.7)	BPD (21.2), SNI (10.6) and treated ROP (3.5).
5. USA, 2016. RS (1998-2011)[12].	357 (47.90)	22-24 (330- 916)	ANS (83.47)	Sepsis (67.22), BPD (57.98), PDA (36.69), ROP (35.57), NEC (23.52), IVH (20.16) and PVL (8.96).
6. Finland, 2019. RS (2007-2015)[10].	2,627 (7.84)	27.9 (1,062)	ANS (95.5)	BPD (21.0), SNI (9.0) and treated ROP (3.6).
7. France, 2018. RS (2011)[13].	783 (30.27)	22-26 (700-890)	ACS and magnesium sulfate.	Severe BPD 129 (16.47), severe IVH 57 (7.27), severe ROP 28 (3.57) and severe NEC 3 (0.38).
8. France, 2018. PS (2011)[14].	427 (52.93)	22-25 (630-1,043)	AB (93.5), ACS (68.7), tocolysis (57.7) and magnesium sulfate (3.1)	Cerebral palsy and severe morbidity (56.6), IVH grades III-IV, cPVL, NEC stages II-III, ROP stage 3 and severe BPD.
9. Israel, 2016. RS (2007-2010)[11].	4,481 (13.88)	28.1 (1,066)	ANS (76)	IVH grade >3 / PVL (15), BPD (14), IVH grade >3 (12), PVL (5) and ROP (3).
10. Israel, 2019. RS (2007-2015)[10].	10,050 (13.54)	28.1 (1,065)	ANS (78.6)	SNI (14.1), BPD (14.0) and treated ROP (3.1).
11. Italy, 2019. RS (2007-2015)[10].	1,465 (11.40)	28.2 (1,048)	ANS (88.6).	SNI (13) BPD (10.8) and treated ROP (3.3).
12. Japan, 2021. RS (2003-2012)[15].	6,898 (14.45)	23.2-25.2 (585-904)	Oxygen, treatment for PDA (57.08), treatment for ROP (32.63) and life support.	PDA (57.08), BPD (34.82), treated ROP (32.63), IVH (22.57), sepsis (11.03), cPVL (3.14) and NEC (1.98).
13. Japan, 2016. RS (2007-2010)[11].	12,608 (5.04)	27.8 (1,008)	ANS (49)	BPD (19), ROP (16), IVH grade >3/PVL (8), IVH grade >3 (4) and PVL (4).
14. Japan, 2019. RS (2007-2015)[10].	30,343 (4.17)	27.8 (1,012)	ANS (56.8)	BPD (23.2), treated ROP (14.3) and SNI (7.0).
15. Korea, 2018. CR (2012)[16].	1 (0.00)	21 (490)	Prophylactic AB, tocolytics, positive ventilation, prophylactic SF and PN.	Comorbidity: PDA, IVH, ROP and sepsis.
16. Korea, 2017. RS (2001-2011)[17].	382 (21.20)	23-26 (583-885)	ANS (77.74)	Sepsis (4.18), BPD (3.40), IVH (3.40), NEC (2.35), ALS (2.09), pulmonary hemorrhage (2.09), PH (1.57) and AKI (0.52).
17. Korea, 2019 RS (2014-2016)[18].	574 (53.66)	23-24 (532-760.2)	ANS (75.78)	Causes of death: sepsis (10.97), pulmonary hemorrhage (6.27), RDS (6.09), BPD (4.87), neurological cause (4.87), ALS (4.35), NEC (3.83), pulmonary hypertension (2.26), PH (1.21) and SIP (1.04).
18. Mexico, 2016. PS (2016)[19].	11 (90.91)	24-25.6 (385-725)	Resuscitation (100) and intensive care.	Comorbidity: RDS (100), neonatal sepsis (63.6), anemic syndrome (27.2), fluid and electrolyte disorder (27.2), hyperbilirubinemia (27.2), hypoglycemia (27.2), IVH (27.2), septic shock (27.2), PDA (18.1) , BPD (9.1), renal failure (9.1), NEC (9.1) and DIC (9.1).
19. Mexico, 2021. RS (2015-2016)[20].	47 (19.15)	≤34 (≤1,500)	ACS, resuscitation, mechanical ventilation (82.97) and surfactant (80.85).	Causes of death: RDS (87.23), neonatal sepsis (85.10). Comorbidity: hyperbilirubinemia (53.19), congenital heart disease (42.55), BPD (38.29), IVH (31.91), NEC (19.14), PDA (17.02) and ROP (14.89).
20. Mexico, 2019. RS (2010-2014)[21].	52 (38.46)	25-34 (<500-<1,000)	PN (100), mechanical ventilation (84) and SF (69.2).	Causes of death: Pulmonary hemorrhage (7.69), IVH (7.69), septic shock (7.69), AKI (5.76), prematurity (3.84), cardiogenic shock (1.92), RDS (1.92) and DIC (1.92). Comorbidities: RDS (84.61), early sepsis (78.84), BPD (59.61), growth restriction (50), IVH (46.15%) and NEC (19.23).
21. Mexico, 2016. RS (2014-2015)[22].	74 (67.57)	20-37 (<600-1,000)	Resuscitation (51.35), SF (51.35), ACS (45.94) and AB (18.91).	Sepsis (17.56), pneumonia (13.51), growth restriction (5.40), IVH (5.40), BPD (4.05), AKI (2.70) and congenital hypothyroidism (1.35).
22. Spain, 2016. RS (2007-2010)[11].	8,063 (16.94)	28.1 (1,061)	ANS (84).	BPD (15), IVH grade >3/PVL (15), IVH grade >3 (10), PVL (6) and ROP (4).
23. Spain, 2019. RS (2007-2015)[10].	18,257 (15.24)	28.1 (1,059)	ANS (88.1).	SNI (15.8), BPD (15.8) and treated ROP (5.6).
24. Sweden, 2016. RS (2007-2010)[11].	2,184 (7.65)	27.8 (1,059)	ANS (82).	BPD (20), IVH grade >3/PVL (7), IVH grade >3 (5), ROP (4) and PVL (2).
25. Sweden, 2018. RS (2006-2015)[23].	40 (47.50)	22.5 (489 ± 62)	SF (100), tocolytics (91) and CC or epinephrine (3).	BPD (52.5), ROP (25), PDA (22.5), NEC (5) and IVH / PVL (5).
26. Sweden, 2019. RS (2007-2015)[10].	5,351 (7.76)	27.7 (1,054)	ANS (82.5).	SNI (7.5), treated ROP (4.5) and BPD (23.6).
27. Switzerland, 2016. RS (2007-2010)[11].	2,034 (10.23)	28 (1,052)	ANS (89).	BPD (13), IVH grade >3/PVL (9), IVH grade >3 (8), PVL 49 (2) and ROP 34 (2).
28. Switzerland, 2019. RS (2007-2015)[10].	4,895 (9.48)	28 (1,045)	ANS (92.0).	BPD (13.7), SNI (8.3) and treated ROP (1.3).
29. UK, 2016. RS (2007-2010)[11].	10,325 (10.31)	27.8 (1,046)	ANS (82).	BPD (32), IVH grade >3 (32), IVH grade >3/PCL (7), PVL 157 (2) and ROP 229 (2).
30. UK, 2019. RS (2007-2015)[10].	38,131 (9.80)	27.8 (1,047)	ANS (88.7).	BPD (37.1), SNI (7.8) and treated ROP (4.1).
	221,883 (9.85)			

AB: Antibiotic; ACS: antenatal corticosteroids; AKI: acute kidney injury; ALS: air leak syndrome; ANS: antenatal steroid; BPD: bronchopulmonary dysplasia; CC: chest compressions; cPVL: cystic periventricular leukomalacia; CR: case report; DIC: disseminated intravascular coagulation; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PH: pulmonary hypoplasia; PN: parenteral nutrition; PS: prospective study; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity; RS: retrospective study; SF: surfactant; SIP: spontaneous intestinal perforation and SNI: severe neurologic injury: grade 3 or greater peri-intraventricular hemorrhage, WG: weeks of gestation.

Using Excel, the data for each article was entered regarding the country of origin, number of newborns included and percentage of mortality, and then a map was made. Countries with more than one article selected and showing consistent data were Australia / New Zealand, Canada, Israel, Spain, Switzerland and the UK.

Extrapolating the information from the gestation week reports that included the different articles consulted, a mean of 27 WG gestation (range 20-37) was estimated . About the weight, the mean was 942.7 g (range 385-1500).

4. DISCUSSION

A clear variation was observed in the mortality percentages for each country. Among the relevant parameters, higher mortality in male and female could not be established due to the lack of data in the studies, however, it has been reported that there is a greater trend in male mortality, in extremely premature infants and low birth weight, if compared with female, since the males presents worse results in the short and long term[24,25].

Information about the survival rates among newborn babies by gender was not available in the resources selected. However, the majority of those who did analyze this factor reported a worse prognosis for the males[11]. From what is shown in different countries, mortality in extremely premature infants has decreased slightly, presumably in part due to the availability of adequate technological resources9. In fact, because of the higher success rate that has been achieved, high-income countries have shifted the definition of preterm birth to earlier gestational ages compared to low-middle-income countries[26].

One difficulty in obtaining homogeneous conclusions by country is that in countries where there is no single universal, public and free healthcare system (Mexico, USA, etc.), the results will be limited by access to the best hospitals.

Among the most used prenatal therapies, the literature consulted reports the administration of tocolytics (corticosteroids/steroids, prophylactic antibiotics, and magnesium sulfate) that benefit the fetal maturation process, thus preventing morbidities associated with mortality in these patients.

Among the most frequent morbidities are BPD, neurological injury (IVH and PVL), ROP, NEC, and CAP. Therapy to prevent BPD includes caffeine, vitamin A, and corticosteroids; however, the use of the latter has been limited due to possible adverse effects on the central nervous system (CNS)[27,28].

The immediate neonatal measures for the neonates in this review were: admission to the neonatal intensive care unit (NICU), mechanical ventilation, administration of prophylactic surfactant, administration of epinephrine, and cardiac compressions,[10-15,17-23].

In the literature there is a tendency to offer intensive care to neonates strictly ≥24 SDG, with the interval between 23 and 24 WG being a grey area with low survival. There is variation concerning local legislation, resources, costs, and ethical dilemmas. GA is considered the best characteristic to estimate survival, but it is suggested to consider other prognostic factors such as weight, sex, and fetal development, given the inaccuracy to determine it and the risk of bias[29,30].

In Japan intact survivors ≥22 WG are reported. The data suggest that the guidelines of the perinatal management provided should be applied: prevention of hypothermia, milking of the umbilical cord for blood culture and complete blood count, respiratory management with continuous positive airway pressure, the surfactant of therapeutic use in RDS, initiation of breastfeeding a few days after birth with subsequent fortification, treatment of CAP, serial cranial ultrasound on days 1, 3, 7, 14, and 30 with expert neurological evaluation and prophylaxis with fluconazole to a state full feed. Discharge indications include a postmenstrual age of at least 35 weeks, adequate growth, stable body temperature, and oxygen saturation, it is important to note that Japan has protected infants ≥22 WG since 1991[31].

In order of frequency, the conditions related to the cause of death within this review are BPD, RDS, sepsis, neurological injury; HIV and LPV, NEC, and congenital heart disease compressions,[10-15,17-23]. Survival with higher prematurity was recorded in Korea with a female newborn of 21 WG30. The lowest mortality percentages correspond to Japan (4.17%) in neonates with a mean of 27.8 WG, Sweden (7.65%) with 27.8 SDG, and Finland (7.84%) 27.9 SDG, being the cases for each country, 30,343; 2,184 and 2,627 respectively (11,12). The highest mortality percentages correspond to France (52.93%) in neonates of 22-25 WG, Korea (53.66%) in neonates of 23-24 WG, and Mexico (90.91%) in neonates of 24-25.6 WG, however, the number of cases for each country should be considered, being 427, 574 and 11 respectively[14,18,19].

The wide disparities between studies from the same countries could partially be explained by a heterogeneous health system. Studies with the higher WG have lower mortality rates, suggesting that WG is the most important factor. On the other hand, each country has different therapeutic approaches, legal and ethical frameworks, and may offer proactive therapy or palliative care.

One key limitation in this study was the lack of current information on extreme prematurity, especially in Latin American and the Caribbean. In addition, another limitation is the economic disparity among the countries analyzed since it is a condition for accessing the necessary technology and medicines that allow increasing the survival of extremely premature babies. The lack of information on other causes such as cultural differences, physicians' bias, national guidelines or health infrastructure, should also be considered as limitations.

4.1 Conclusion

The mean gestational age included in this analysis was between 26.13 and 27.55 weeks of gestation and the mean weight had a mean of 868.4 g for the lowest values and 981.5 g for the highest. When compared with other countries that have registry networks for pre-term infants, low-income countries do not have an extensive and detailed database on mortality rates or the resources to manage premature infants to adequately calculate the epidemiological characteristics during this period. Good practices suggest that in order to improve the management of preterm infants, countries with high mortality rates should implement the systematization of the information registry and the development of their own technology. The definition of fetal viability and the consequent medical efforts made to care for a newborn may be self-limiting, creating a vicious circle in which nothing more is done because it is thought that better results cannot be obtained.

The management of periviable births is a grey area for doctors and parents when making decisions about the termination of pregnancy, neonatal resuscitation, and the administration of palliative care, which is why parameters other than GA must be analyzed, in addition to the shared decision of the parents.

Recommendation

The authors recommend that each medical unit analyze its infrastructure and the capacity of its specialists to provide an opportunity to treat extremely premature babies. The priority needed to improve the survival of extremely premature babies is that the technology required for their care must be more accessible in all countries[32].

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