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Global inequities in the survival of extremely preterm infants: a systematic review and meta-analysis

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Abstract

Background Despite the associated major morbidities, advances in neonatal care units have improved the survival rates of extremely preterm infants. However, the varying survival rates make it challenging to set policy decisions around the standardization of care. Therefore, this study aimed to determine the global survival rate of extremely preterm infants and to compare it across different income levels and over time during the last two decades.

Method A comprehensive systematic search was conducted across major databases, including PubMed/Medline, EMBASE, CINAHL, Web of Science, Scopus, AJOL, Google Scholar and Google, to identify relevant articles. All peer-reviewed studies reported the survival rate of extremely preterm infants (born before 29 weeks' gestation) between January 1st, 2000, and June 25th, 2024, were included. Outcomes were compared between Epoch 1 (2000–2015, Millennium Developmental Goals period) and Epoch 2 (2016–2024, Sustainable Developmental Goals period). DerSimonian–Laird random effects model was fitted to estimate the pooled weighted outcomes.

Results A total of 217 studies involving 917,176 infants were included. Based on published data, 61.4% (95% CI: 58.13–64.81) of extremely preterm infants survived to discharge, and 51.7% (95% CI: 44.25–59.22) of survivors were discharged without major morbidity. Survival rate was significantly lower in low- and middle-income countries (44.3%) compared to high-income countries (69.3%). Among low- and middle-income countries, survival improved from 38% during the epoch 1 to 44.8% during the epoch 2. While in high-income countries it was 69.9% during epoch 1 and 64.2% during epoch 2. These findings are based on reported literature; may not fully reflect outcomes in low-resource settings where data are limited and underreported. Variability in the inclusion and care of borderline viable infants also contributes to the heterogeneity and uncertainty of the estimates.

Conclusion Survival of extremely preterm infants varies widely across settings, with fewer than half surviving in low- and middle-income countries. While some improvement was observed in these regions during the Sustainable Developmental Goals period, comparisons across epochs and regions should be interpreted cautiously due to differences in data availability and population characteristics. These variations underscore the need for context-specific strategies that balance available resources, cultural values, and ethical considerations. Further population-

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level data, particularly from low-and middle-income countries, are essential to inform equitable global neonatal care policies.

Registration PROSPERO (CDR42023447612 (PROSPERO (york.ac.uk)).

Clinical trial number Not applicable.

Keywords Survival rate, Extremely preterm infant, Meta-analysis

Introduction

Preterm birth is a significant global public health concern [1]with an estimated 13.4 million neonates born preterm annually [2]. It is the leading cause of mortality in children under five years of age [3]. In 2021, preterm birth complications accounted for more than one-third of the 2.3 million neonatal deaths and almost one million under five child deaths worldwide [4]. Extremely preterm infants (EPIs) (born before 28 weeks) cannot survive without the support of quality specialist neonatal care. They have significantly higher morbidity and mortality rates than other preterm births do, despite comprising just 5% of cases [5–7]. These births are associated with increased risks of major short-term morbidities, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), severe intraventricular haemorrhage (IVH), and severe retinopathy of prematurity (ROP) [8, 9]. Long-term concerns include lifelong disabilities such as cognitive impairment, cerebral palsy, blindness, deafness [10, 11] and compromised quality of life [12, 13].

Despite advancements in neonatal intensive care unit (NICU) technology and therapy, EPI survival rates vary significantly across income levels [14, 15] exceeding 90% [16], compared with approximately 10% in low-income countries [7]. Recent data revealed a 39% survival rate in developing nations [17] and an 83.6% survival rate in Europe [18]. Globally, studies on the survival of EPI have shown significant inconsistencies [11, 19, 20] with rates ranging from 7% [21] to 92.6% [22]. These disparities both between and within countries [23] are influenced by differences in healthcare [24] viability definitions [25] and attitudes toward lifesaving support [26]. This makes it difficult for scientific committees and health policy authorities in countries with varying income levels to translate this information for clinical decision-making, benchmarking and prioritizing future interventions. Therefore, synthesizing survival data from published studies across different regions can provide valuable insights into current trends and gaps, while highlighting the need for more comprehensive, population-based data to guide future strategy development and implementation.

Reducing neonatal and under five child mortality rates is a key objective of the Millennium (2000–2015) and Sustainable Development Goals (2016–2030). Sustainable Development Goal 3.2 aims to reduce neonatal deaths to less than 12 per 1,000 live births and under five child deaths to less than 25 per 1,000 live births by 2030 [27]. Previously, the Millennium Developmental Goal 4 aimed to reduce under five mortality by two-thirds by 2015 [28]. While Millennium Developmental Goal 4 focused on the rate of improvement, Sustainable Development Goal 3.2 establishes absolute mortality thresholds, aiming to sustain and standardize progress globally.

Therefore, this systematic review and meta-analysis aimed to provide updated global survival rate and survival without major morbidity among EPI. It also compared these rates across low-, middle-, and high-income countries, examining their progress during the Millennium Developmental Goals period and Sustainable Development Goals period.

Methods

This systematic review and meta-analysis protocol is registered at PROSPERO (CDR42023447612; PROSPERO (york.ac.uk)). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [29] was followed to report this systematic review and meta-analysis (**Additional file 1**).

Eligibility criteria

Study scope and context

This review included all peer-reviewed observational studies on EPI born from January 1st, 2000, to June 25th, 2024 and reported on survival to discharge of this population. While the WHO defines EPIs as babies born before 28 weeks, we included those born before 29 weeks to align with most primary studies (categorizing them as EPIs). Only studies that reported outcomes based on gestational age were included to ensure consistency and comparability across included data. Studies in any language were eligible if Google language translations were available [30–33]. Our study focused on the survival rate and survival without major morbidity and our primary objective was to extract numerical data such as sample sizes, prevalence rates from the articles. This type of data is less prone to misinterpretation during translation, as numbers and associated terminology are generally consistent across languages.

Exclusion criteria

Qualitative studies, case-control studies, case reports, systematic reviews, meta-analyses, scoping reviews, case

selective studies that had specific exclusion criteria, and studies without full texts like conference abstracts (difficult to assess their quality) were excluded from this study. To avoid duplication, when multiple studies reported data from the same neonatal networks or large databases, we included only the most recent and comprehensive reports that were most relevant to our objectives, in the case of historical comparative cohorts too. Unpublished studies, studies assessed using parent recall, and those on preterm neonates born after 29 weeks were also excluded.

Outcome of the study

The primary outcome of this review was to determine the pooled survival rate of EPI globally. For comparison purpose, data from primary studies were grouped by regions, World Bank income classification (income grouping reflect the classification as of 2023), and epochs: Millennium Development Goals period (MDGP)-epoch 1 (2000–2015) versus Sustainable Development Goals period (SDGP)-epoch 2 (2016–2024), this developmental period isn't capped at 2024, but our search for articles extended up to that year. We utilized this year classification because different global interventions and strategies were implemented during these distinct and well demarcated periods to improve neonatal and child health. To analyse survival and survival without major morbidity by specific gestational age (22–28 weeks), we utilized a decade-based classification (2000–2009 vs. >2009) rather than the primary epoch definitions used elsewhere in the study. This allowed as to include a greater number of comparable studies within each group and to enable meaningful, interpretable comparisons of GA-specific outcomes across time.

In this meta-analysis, the survival to discharge rate of EPI was considered the number of infants discharged to home alive irrespective of the time (discharged from the hospital at any time or at one year) and denominators. This study also aimed to estimate the survival without major morbidity of EPI, calculated as the proportion of EPI neonates who survived to discharge without major morbidity to the number of EPI infants who survived to discharge. The survival rate might be calculated based on three denominators as follows:

1. The survival rate among all extremely preterm live birth neonates was considered the proportion of the number of survivors at hospital discharge to the number of extremely preterm live births.
2. Survival rate among live-born EPIs admitted to the NICU was defined as the proportion of infants who survived to hospital discharge out of all live-born EPIs admitted to the NICU.
3. The survival rate among actively treated live EPIs was considered the proportion of the number of survivors at hospital discharge to the number of live EPIs actively treated.

Major neonatal morbidity was considered if surviving EPI had any of the following complications:

BPD was defined as the need for supplemental oxygen and/or respiratory support (intermittent mandatory ventilation, continuous positive airway pressure or high flow) at 36 weeks postmenstrual age (severe); Grade 3 or 4 IVH associated with ventricular dilatation according to Volpe grading; Stages II and III NEC according to Bell's classification; and Stages three and above ROP and/or requiring laser treatment according to international ROP committee classification criteria. Survival without major morbidity was considered survival to discharge without any of the above major morbidities. The calculation of survival and survival without major morbidity for each specific gestational age (22–28 weeks) was performed in the same manner as mentioned above.

Search strategies

A comprehensive systematic search was conducted by two authors (TG and HKK) up to June 25th, 2024, using medical electronic databases, including PubMed/Medline, EMBASE, CINAHL, Web of Science, Scopus, AJOL (African Journal of Online), Google Scholar and Google, to identify relevant articles. Keywords and subject headings were combined in the search. Snowballing of already identified article references supplemented the electronic database search (supplementary file-Sect. 1).

Screening

After a comprehensive systematic search, potentially eligible studies were imported into Covidence software to manage duplication and further screening. Two independent reviewers (TG and HKK) screened all the articles' titles and abstracts on the basis of the eligibility criteria. The titles and abstracts of potentially eligible studies were subsequently used to access the full text of each article for further screening. Articles lacking full text were excluded if the authors could not be contacted after at least two attempts via email or ResearchGate to obtain full-text access; hence, full text is a prerequisite for quality assessment and data extraction. Then, studies reporting the outcomes for which definition were given and fully accessed during data extraction were considered for the final selection in this review.

Critical appraisal

The quality of the eligible articles was assessed via the Newcastle–Ottawa Scale (NOS) for cohort studies [34]. Studies scoring 7/9 or higher were classified as good

quality (low risk), whereas those scoring below 7/9 were considered poor quality (high risk). Two independent authors critically appraised the studies, and any discrepancy was solved via consensus.

Data extraction

A standardized data extraction format, following the Joanna Briggs Institute systematic review guidelines, was utilized within Covidence software [35] (Supplementary file-Sect. 2). Disagreements between reviewers during data extraction were resolved through consensus. Finally, the extracted data were exported to Stata for further analysis.

Quantitative data synthesis

The descriptive characteristics of the primary studies are summarized in tables and narrative texts. Heterogeneity across eligible studies was assessed and quantified via Cochrane Q statistics and inverse variance (I^2). The extracted data were subjected to meta-analysis after logit transformation to obtain the pooled weighted effect size. A DerSimonian–Laird random effects model was applied to estimate the pooled weighted survival to discharge rate of EPI, as potential heterogeneity was expected. The pooled meta-analysis results with 95% confidence intervals (CIs) are presented in a forest plot. Survival without major morbidity, specific major morbidity, survival, and survival without major morbidity rates for each specific gestational age category were also reported. Subgroup analysis was conducted on the basis of actual geographical location, various region categories, World Bank income level, year of birth (epoch 1 (2000–2015) and epoch 2 (2016–2024)), and specific gestational age (22–28 weeks) to identify the source of heterogeneity. Sensitivity analysis was conducted to assess the impact of individual studies on the pooled meta-analysis. Asymmetric visualization of the funnel plot was used to declare publication bias. All analyses were performed in STATA version 17.

Results

Search results

Among the 9,320 studies initially retrieved, 786 articles underwent full-text review, resulting in the inclusion of 227 primary studies involving 917,176 extremely preterm neonates born before 29 weeks of gestation for this systematic review and meta-analysis (Fig. 1).

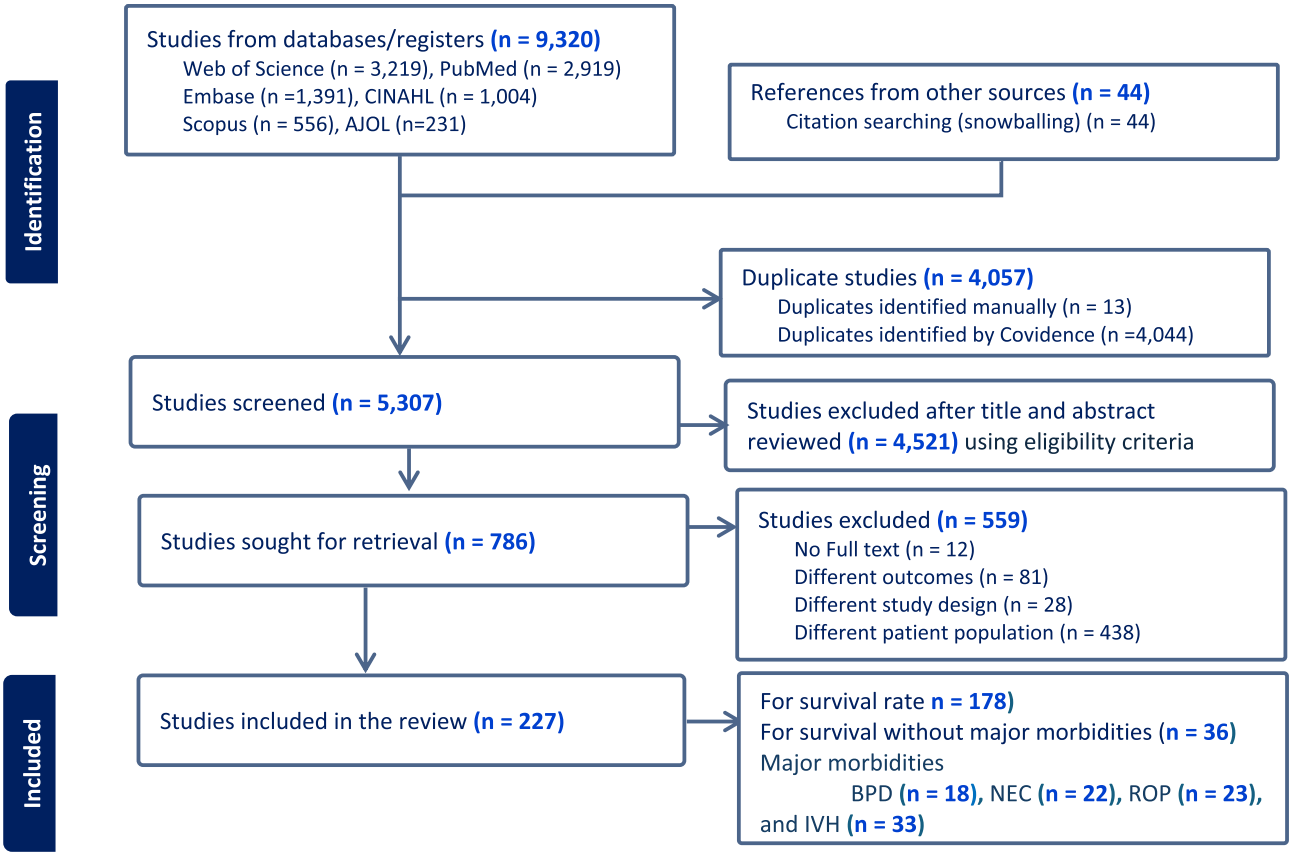

Fig. 1 PRISMA flow chart of search results

Study characteristics

Among the 227 studies, 44 countries were represented. One-third of the studies were from Europe and Central Asia, with East Asia, the Pacific, and North America each contributing 53 articles. Over two-thirds of the studies were conducted in high-income countries (HIC), 12.7% in upper-middle-income countries, 11.4% in lower-middle-income countries and 1.3% in low-income countries (LIC). The studies, published from 2007 to 2024, involved EPIs born between 2000 and 2021 (supplementary file-Table 1).

Risk of bias

Among the 227 included studies, 171 were classified as having a low risk of bias, and 56 were deemed to have a high risk of bias (supplementary file-Table 1).

Survival to discharge rate of EPIs

Finally, data from 178 peer-reviewed articles were analysed to estimate the survival to discharge rate. The overall pooled survival to discharge rate of EPI infants was 61.4% (95% CI: 58.13, 64.81), with considerable heterogeneity across studies ($I^2 = 97\%$, $p = 0.000$) (supplementary file-Fig. 1). A subgroup meta-analysis was conducted to explore sources of heterogeneity, considering factors such as risk of bias, regions, World Bank income levels, year of birth, and denominators (live birth, NICU admission and active treatment).

Low-risk-of-bias studies had a pooled survival rate of 66.6% (95% CI; 63.01, 70.16), whereas the high-risk-of-bias studies had a rate of 47.9% (95% CI; 42.10, 53.87) (supplementary file-Fig. 2). The Mann–Whitney U test revealed significant variation across risk of bias categories ($p = 0.000$). Survival rates differed by income level: 69.3% (95% CI: 66.49, 72.17) in HICs, 55.6% (95% CI: 48.58, 62.78) in upper-middle-income countries, 33.9% (95% CI; 28.28, 39.54) in lower-middle-income countries, and 32.2% (95% CI; 3.77, 60.71) in LICs ($p = 0.000$) (Fig. 2). This distinction was also evident in the pooled survival rates, encompassing only studies with a low risk of bias (supplementary file-Fig. 3).

"This plot includes a large number of studies; zooming in is recommended for optimal readability."

The overall survival rate was lower in epoch 2 (2016–2024), at 49.7% (95% CI; 40.74, 58.67), than in epoch 1 (2000–2015), at 63.1% (95% CI; 58.76, 67.59) (Fig. 3). However, in studies with a low risk of bias, the survival rate was 66.9% (95% CI; 62.37, 71.52) in epoch 1 and 71% (95% CI; 59.26, 82.87) in epoch 2, but this difference was not statistically significant (supplementary file-Fig. 4). In low- and middle-income countries (LMICs), a 38.04% (95% CI: 30.22, 45.85) survival rate was reported during epoch 1, and a 44.87% (95% CI: 35.10, 54.65) survival rate was reported during epoch 2. However, 69.98% (95% CI: 66.87, 73.08) of the survival rate during epoch 1 and 64.19% (95% CI: 49.17, 79.21) during epoch 2 were reported in HICs (only 6 studies were included in epoch 2 and may not reflect the actual survival rate). While high risk of bias studies were retained to provide a comprehensive overview of the literature, their findings were interpreted with caution. These studies might be contributed to the observed heterogeneity and resulted in wider confidence intervals, reducing the precision and reliability of pooled estimates.

The highest survival rates of EPI infants were observed in East Asia and the Pacific (72.9% (95% CI: 68.96, 76.83) and North America (71.9% (95% CI: 65.41, 78.42)). In contrast, the lowest rates were in sub-Saharan Africa (31.3% (95% CI: 24.51, 38.11)) and the Middle East and North Africa (39.7% (95% CI: 32.61, 46.85)) (supplementary file-Fig. 5). Survival rates were consistent across various denominator categories: 65.6% (95% CI; 59.39, 71.94) for live births, 59.6% (95% CI; 55.77, 63.50) for NICU admissions, and 75.9% (95% CI; 70.92, 80.98) for actively treated EPIs (p value = 0.168) (supplementary file-Fig. 6). Sensitivity analysis was performed to assess the impact of primary studies on the overall survival rate, and no significant change was observed in the combined results. Even when studies with small sample sizes were excluded, there was no significant change in the overall effect estimate, as shown in supplementary file Fig. 7.

"This plot includes a large number of studies; zooming in is recommended for optimal readability."

Furthermore, the presence of publication bias was ruled out through a symmetrical funnel plot (supplementary file-Fig. 8) and an insignificant Egger statistical test, with a p value of 0.102.

Survival to discharge without major morbidities of EPI

Among the 71,240 survived EPIs (from 36 studies), 51.7% (95% CI; 44.25, 59.22) were discharged without major morbidities. Significant heterogeneity was observed across the primary articles ($I^2 = 97.4\%$, $p = 0.000$) (supplementary file-Fig. 9). Subgroup analysis on the basis of the risk of bias revealed a 51.8% (95% CI; 43.89, 59.90) rate of survival without major morbidities in the low-risk-of-bias studies and a 49.9% (29.34, 70.58) rate in the high-risk-of-bias studies (supplementary file-Fig. 10). The rates across the year of birth categories (epoch 1 vs. epoch 2) were similar: 55.1% (95% CI; 49.59, 60.71) and 52% (95% CI; 28.44, 75.59), respectively (supplementary file-Fig. 11).

With respect to the World Bank income categories, a higher survival rate without major morbidities was

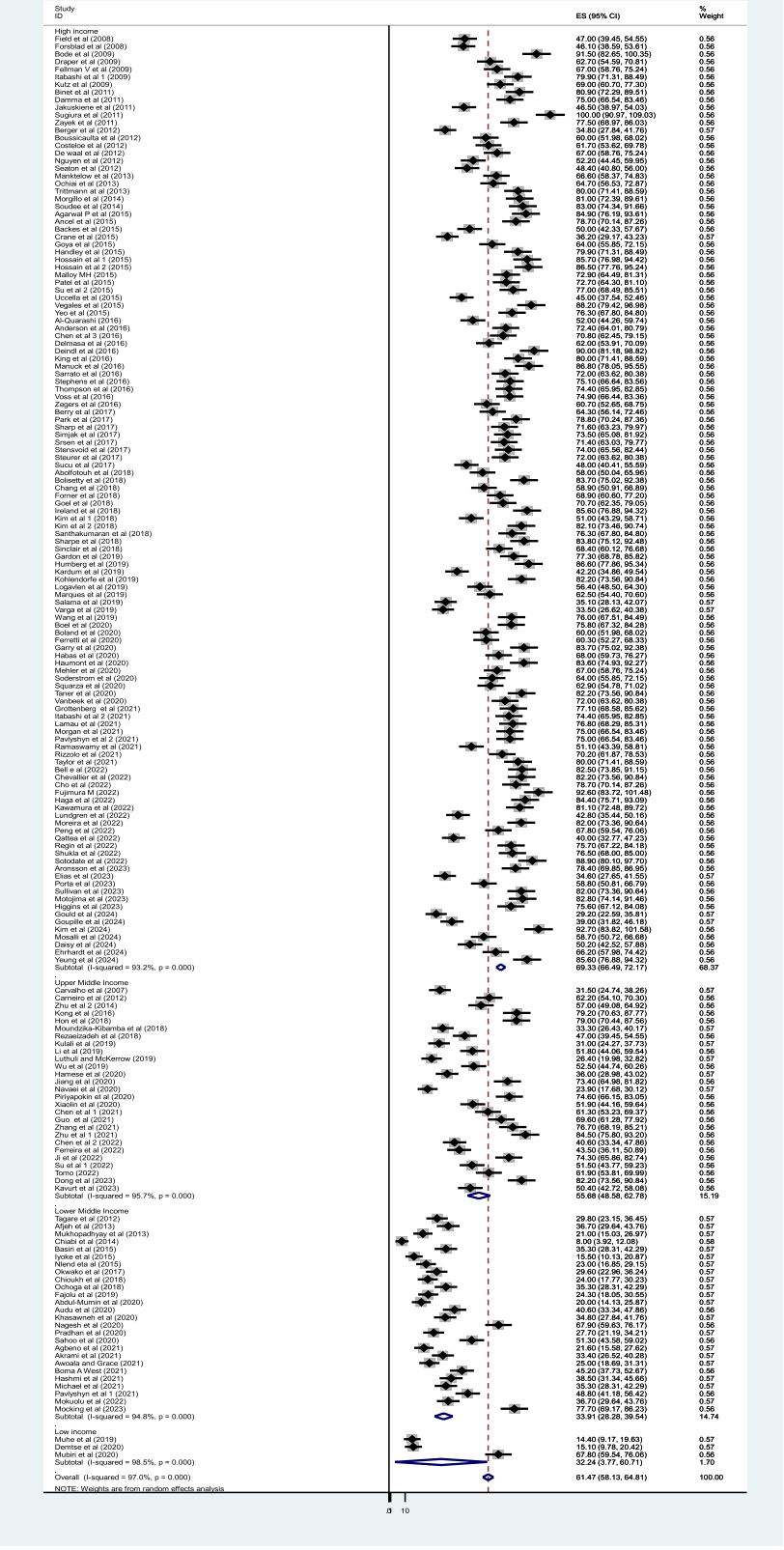

Fig. 2 Forest plot of survival to discharge rate of EPIs by income level from 2000–2024

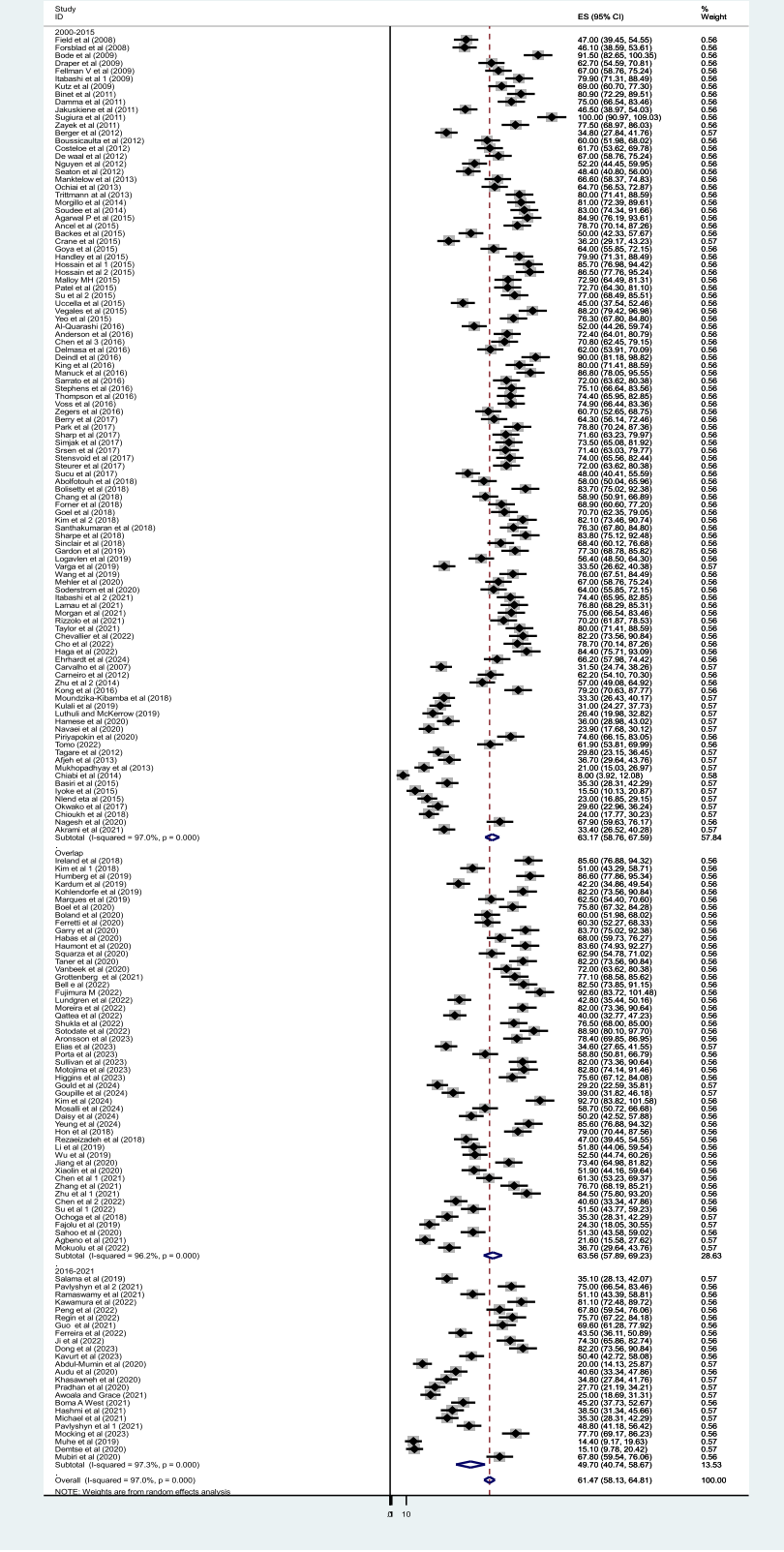

Fig. 3 Forest plot of the survival to discharge rates of extremely preterm infants analysed by year of birth (2000–2015 vs. 2016–2021)

observed in upper-middle-income countries (67.2%, 95% CI; 48.02, 86.42), followed by 49.5% (95% CI; 41.55, 57.55) in HICs and 40% (95% CI; 32.77, 47.23) in a single-centre study in lower-middle-income countries (no studies reported from LICs) (supplementary file-Fig. 12). No publication bias observed across included studies (supplementary file-Fig. 13).

Survival to discharge rate at a specific gestational age (22–28 weeks)

The meta-analysis also estimated the survival rates without major morbidities for each gestational age (Fig. 4).

However, the majority of the studies included to estimate the survival rate at discharge for each gestational age were reported from HICs. With respect to survival without major morbidity rates, the majority were from HICs, few were from middle-income countries, and none were from LICs (supplementary file-Table 2).

A pooled analysis of 46 studies revealed that 27.6% of preterm infants born at 22 weeks gestation survived to discharge globally (95% CI: 19.77, 35.48%). Among these survivors, 14% were discharged without major consequences. A survival to discharge rate of only 41.9% (95% CI; 37.1, 47.01) was reported for preterm infants born at 23 weeks of gestation. Among the 1,318 survivors, only 16.8% were discharged without major morbidities.

Over half of the preterm infants born at 24 weeks of gestation (55.2%, 95% CI; 50.25, 60.08) survived to discharge. Globally, approximately one-third (33.8%) of surviving infants born at 24 weeks of gestation are discharged without major morbidities. Similarly, more than two-thirds of the infants born at 25 weeks of gestational age survived to discharge (70.2%, 95% CI: 64.99, 74.89), and almost half of the 6,476 surviving infants (45.1%) were discharged without major morbidities. A survival-to-discharge rate of nearly 80% was reported among infants born at 26 weeks of gestational age (79.6% (95% CI; 74.92, 83.69)). The survival to discharge without major morbidities rate for infants born at 26 weeks of gestation was 56.7%.

Among the 30,991 infants born at 27 weeks of gestation, 84.4% survived to discharge (95% CI; 79.84, 88.76). Among these surviving infants, 66.1% were discharged without major morbidities. In a pooled analysis of 24 articles including 29,851 infants born at 28 weeks of gestation, the survival to discharge rate was 87.3%, and 69.7% of the infants survived without major morbidities. In general, the survival to discharge rate varied significantly across gestational age categories (p value = 0.001, Kruskal–Wallis test). The mean survival to discharge rate of EPIs born at 23 weeks and 24 weeks increased from 2000 to 2009 to 2010–2024, but this did not exist for other gestational age groups (Fig. 5).

Most of the included studies were from high-income countries and were conducted during the Millennium Developmental Goals period. The publication bias of each respective gestational age survival and survival without major morbidity is presented in supplementary file-Figs. 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

Specific major morbidities among survivors

In general, almost all eligible studies included to pool the effect size of each specific major morbidity were from HICs, with the exception of two articles reported from middle-income countries (One contributed data on NEC, the other on ROP, and both were included in the estimation of BPD rates). Severe BPD was the predominant major morbidity among survivors, with a pooled effect size of 30.8% (95% CI; 22, 39.6) on the basis of 18 primary studies. Its prevalence has increased over the last decade

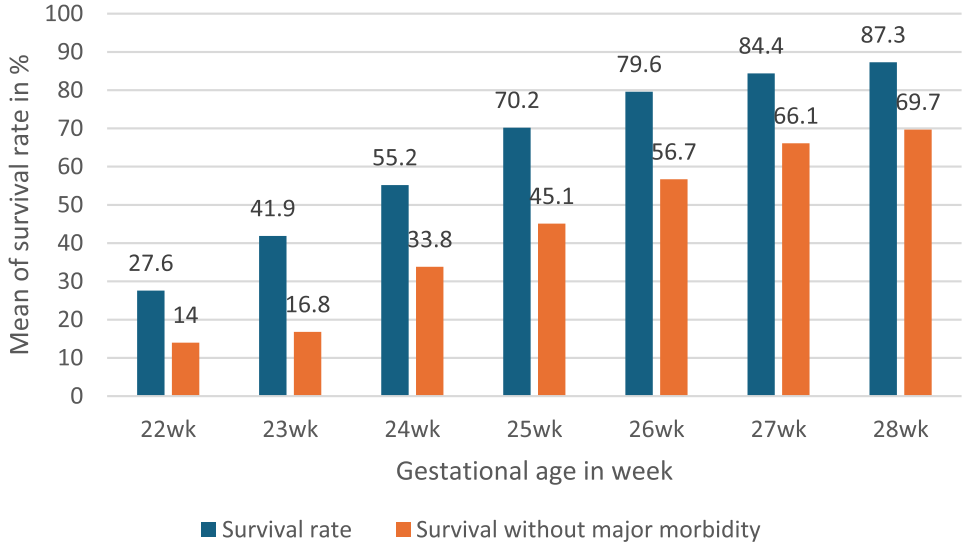

Fig. 4 Survival and survival without major morbidity rates of extremely preterm infants born from 22–28 weeks from 2000–2024

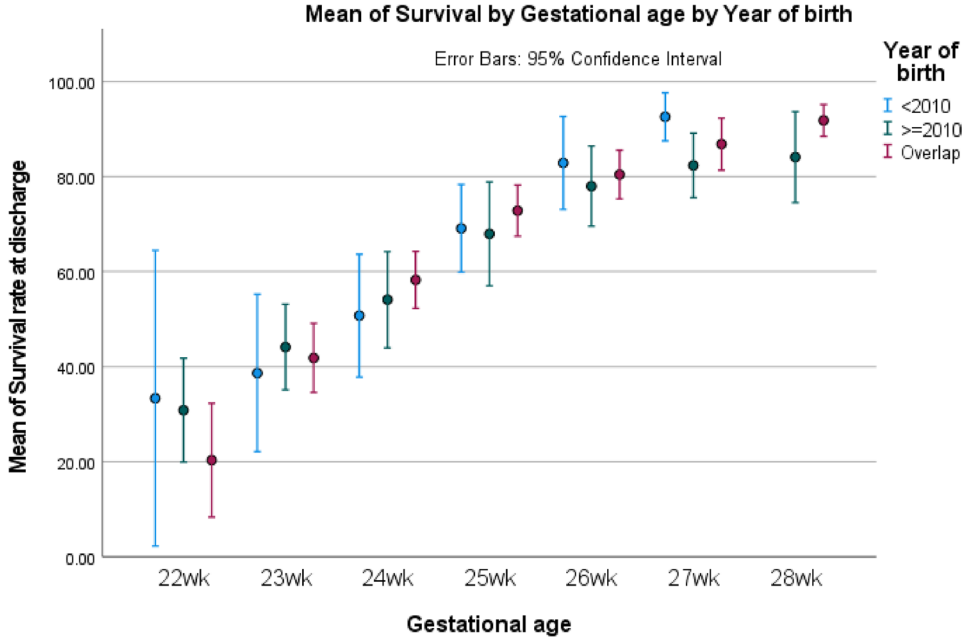

Fig. 5 Survival to discharge rate across gestational age categories by year of birth

(2010–2024) to 32.7%, up from 24.4% in the EPI born from 2000 to 2009. ROP is the second most reported major morbidity. On average, 21.1% (95% CI; 15.9, 26.3) of EPI survived to discharge with severe ROP. Notably, the prevalence of severe ROP decreased from 19.2% from 2000 to 2009 to 15.3% from 2010 to 2024.

According to pooled analysis of 33 studies, 11.1% (95% CI; 9.3, 12.9) of survived EPI experienced severe IVH at discharge, with a decrease from 14.5% from 2000 to 2009 to 9% in 2010 and later. With respect to NEC incidence, 6.1% of surviving EPIs were diagnosed with severe NEC at discharge, with a consistent prevalence of approximately 4.9% from 2000 to 2009 and 4.8% from 2010 to 2024. In general, the prevalence of each major morbidity among survivors decreased from 2000 to 2009 to 2010–2024, except for severe BPD. All the data related to the incidence of major morbidities and improvements over time are presented in Supplementary file-Figs. 2626, 27, 28, 29 and 30. The publication bias across each major morbidity is reported in Supplementary file-Fig. 31.

Certainty of evidence (CoE)

To rate the quality of evidence synthesized in our systematic review and meta-analysis, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was applied. Accordingly, the extent of confidence in our estimated effect size ranges from very low to moderate evidence of effect size (Table 1).

Discussion

In our analysis, the overall survival to discharge rate of preterm infants born before 29 weeks of gestation was 61.4%, with considerable heterogeneity. The heterogeneity across the included articles might be explained by the inclusion of studies around the globe characterized by diverse variations in population background, geographical area, and clinical practice. More specifically, inadequate descriptions of factors such as high-order pregnancy, methods of gestational age calculation, congenital anomalies, and intensive treatment probably affect the survival rate variations among individual studies [36, 37]. Although we are moderately confident in the pooled effect estimate based on the published literature, we acknowledge that these results are not derived from population-based data and may underrepresent extremely preterm infants in the lowest-resource settings where reporting is limited or absent.

Although 56 studies were assessed as having a high risk of bias, they were included in the primary analysis to ensure comprehensive representation of global survival data across time and settings. Excluding these studies would have disproportionately limited data from earlier epochs and lower-resource regions. Subgroup analysis by risk of bias showed that the overall decline in survival observed in epoch 2 (compared to epoch 1) was not present among low risk-of-bias studies, where survival was slightly higher than epoch 1, though not statistically significant. This suggests that the observed decline may reflect differences in populations or reporting methods rather than true deterioration in care. Including all studies, with stratified analysis by risk of bias, allowed a

Table 1 Certainty of evidence of the outcomes of this study

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	CoE
Survival	Not serious	Not serious	Not serious	Not serious	None	Moderate
Survival without major morbidity	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival at 22wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival without major morbidity at 22wk	Not serious	Serious[1]	Not serious	Serious[2]	---	Very low
Survival at 23wk	Not serious	Not serious	Not serious	Serious[2]	None	Low
Survival without major morbidity at 23wk	Not serious	---	Not serious	Not serious	None	Low
Survival at 24wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival without major morbidity at 24wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival at 25wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival without major morbidity at 25wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival at 26wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival without major morbidity at 26wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival at 27wk	Not serious	Serious[1]	Not serious	Not serious	None	Low
Survival without major morbidity at 27wk	Not serious	Serious[1]	Not serious	Serious[2]	None	Very low
Survival at 28wk	Not serious	Serious[1]	Not serious	Serous[2]	None	Very low
Survival without major morbidity at 28wk	Not serious	Serious[1]	Not serious	Serious[2]	---	Very low
Severe BPD	Not serious	Serious[1]	Not serious	Serious[2]	None	Very low
Severe ROP	Not serious	Serious[1]	Not serious	Not serious	None	Low
Severe IVH	Not serious	Serious[1]	Not serious	Not serious	None	Low
Severe NEC	Not serious	Serious[1]	Not serious	Not serious	None	Low

NB: [1]Serious Inconsistency-Substantial heterogeneity across studies and variability in effect sizes not fully explained by subgroup analyses. [2]Serious Imprecision-Wide confidence intervals and/or small sample size in subgroup analyses, affecting certainty of effect estimates

more nuanced interpretation of trends. Notably, the lowest survival rates were reported in low-income country during epoch 2 [38–40], while relatively few high-income country studies were published in the same period. and only a few reports were published during epoch 2 in high-income countries.

An improvement in the survival rate was observed in LMICs from epoch 1 to epoch 2, whereas in HICs, a low survival rate was reported during epoch 2 compared to epoch 1. The observed decrease in survival rates in HICs during epoch 2 may be attributed to evolving clinical practices and changes in the population of infants receiving active care. Over time, there has been a shift towards offering active treatment to more previable infants, particularly those born at 22 weeks' gestation, who were previously considered non-viable. This expansion of care to more vulnerable subpopulations likely contributed to the observed decrease in overall survival rates in these settings, not due to a decline in care quality, but due to a change in the denominator population being treated. The survival rates for infants born at 22 weeks varied significantly across centres, largely depending on the aggressiveness of care provided [24]. Therefore, the inclusion of more high-risk infants in active care protocols during epoch 2 may have influenced overall survival rates, reflecting changes in clinical decision-making and ethical considerations.

A significant variation in survival to discharge rate was observed across high-income and low- and middle-income countries [17] highlighting unacceptable inequities. Similarly, a meta-analysis highlighted a significant disparity in survival rates, with improvements overtime but persistent inequalities between high-income and low-to middle-income countries [41]. The management of EPIs varies across and within countries, influenced by differences in national policies, resource availability, cultural attitudes and ethical considerations [42, 43]. In HICs, there are established guidelines that support active treatment for infants born as early as 22–24 weeks' gestation. For instance, the American College of Obstetricians and Gynaecologists defines previable birth as occurring between 20 and 25 weeks' gestation, with recommendations for individualized care based on gestational age and other factors [44]. Similarly, countries like Japan and Sweden have reported survival rates of 58–63% for infants born at 22 weeks, reflecting their proactive approaches to neonatal care [45, 46].

Conversely, in LMICs, the approach to managing EPIs is often constrained by limited resources and infrastructure. Thus, gestational age thresholds for viability in LMICs are typically higher, often around 28–29 weeks, due to challenges such as inadequate neonatal intensive care facilities and limited access to life-saving interventions [47]. Furthermore, within both HICs and LMICs, there is considerable variability. For example, in the Netherlands, guidelines recommend a more conservative approach to resuscitating infants born at the threshold of viability, emphasizing shared decision-making with parents [48]. In LMICs, disparities between urban and rural healthcare settings can lead to inconsistent application

of neonatal care protocols [49]. These variations underscore the complexity of establishing universal guidelines for the care of EPIs and highlight the need for context-specific policies that consider local resources, cultural values, and ethical frameworks. Therefore, in resource limited setting, prioritizing cost-effective interventions such as kangaroo mother care, breastfeeding support, thermoregulation, and infection prevention remains critical for improving outcomes across all gestational age groups. A careful balance is needed to ensure that efforts to improve EPI survival do not divert limited resources away from these broader, high-impact strategies.

The survival rate of EPI varies significantly by region, with the highest rates reported in North American and East Asia and the Pacific and the lowest rates reported in sub-Saharan Africa, followed by the Middle East and North Africa. Variation in attitudes and decisions regarding lifesaving support for EPI is the common reason for this variation [50]. Limited access to cost-effective care such as thermal support, breastfeeding assistance, and respiratory care in LICs along with suboptimal use of available technology in middle-income settings, further exacerbates these differences [24, 51]. Higher survival rate was reported among EPI actively treated followed by live births and NICU admitted infants. In some settings, NICU admission may include infants receiving only palliative or short-term care, particularly at the lowest gestational ages, leading to lower survival rates in this group. In contrast, actively treated infants often represent a selected subgroup with better prognosis. Variations in clinical practices, reporting, and treatment thresholds across studies and regions further limit direct comparability between these groups.

As gestational age increased, the survival rate at discharge also increased. This could be because infants born at lower levels of viability are at greater risk of vulnerability and because of the varying attitudes of health care professionals and parents in optimism toward providing lifesaving services and resource availability. With respect to the survival rate by year of infants born at each gestational age epoch, only the survival rate of neonates born at 23 and 24 weeks improved from epoch 1 (2000–2009) to epoch 2 (2010–2024).

Only half of the surviving EPI were discharged without major morbidity, even though most of the studies were from HICs. As gestational age increases, a significant improvement in survival without major morbidity and a decrease in mortality are also observed. Advances in technology and therapies improve survival of EPI, but morbidity remains a significant threat, increasing the risk of lifelong disability and reducing quality of life. Clinical decisions should prioritize the infant's best interests, weighing the burden of intensive care, including 'pain and suffering', against the expected outcome [52].

Additionally, this meta-analysis revealed that severe BPD was the most frequently diagnosed major morbidity among survivors, followed by severe ROP, severe IVH and severe NEC. This finding is in line with a systematic review and meta-analysis of the global incidence of BPD, which reported a range of 10–89% [53]. While rates of other major morbidities such as IVH, and NEC have decreased over time likely due to improvements in neonatal care practices including antenatal steroid use, enhanced infection prevention, and better nutritional strategies [54]. BPD rates have shown an increasing trend. This may be explained by the improved survival of EPIs who are at the greatest risk for BPD. Moreover, prolonged use of respiratory support and oxygen therapy, necessary for survival in these vulnerable infants, may also contribute to the increased incidence of BPD [55]. Therefore, the increase in BPD may reflect a shift in morbidity patterns due to enhanced survival rather than a deterioration in care quality.

It is important to recognize that many LMICs do not routinely provide active care for infants born below 26–28 weeks of gestation, often due to limited resources and infrastructure. Therefore, the inclusion of LMIC data in this review is not intended to advocate for immediate extension of care to the most EPIs in these settings, but rather to provide a global perspective on outcomes. Efforts to improve survival in LMICs should be prioritized at higher gestational age thresholds, where mortality remains high and interventions are more likely to be feasible and impactful. The underrepresentation of LMIC studies likely reflects broader challenges in research infrastructure, funding, and publication access in these settings. Barriers such as limited research capacity, underreporting, and language or indexing bias may all contribute to the lack of available data. This highlights the need for targeted investment in research in LMICs to inform context-appropriate policy and practice.

Limitations of the study

While this study is a large global systematic review and meta-analysis to estimate survival and survival without major morbidity to the discharge rate of EPI, it has limitations. The use of Google Translate for translating non-English articles may pose a limitation due to potential inaccuracies in language translation, though this is mitigated by our focus on extracting numerical prevalence data, which is less affected by contextual nuances. Considerable heterogeneity was found across the included studies for the pooled outcomes. Nevertheless, we are moderately confident in the pooled effect estimate of survival to discharge rate, and the true effect is likely to be close to the estimated effect based on published data. The certainty of evidence for all other outcomes ranged from very low to low. The overwhelming majority of included

studies were from HICs, with a small number representing middle-income settings and only few from low-income countries, where health systems, resources, and patient populations may differ substantially. As a result, the pooled estimates presented here may not be generalizable to LMICs, where neonatal outcomes may differ substantially due to variation in access to antenatal corticosteroids, skilled birth attendance, intensive care, and follow-up care. This highlights a critical need for more high-quality data from LMICs to inform global neonatal health policy. In addition, most included studies are not population-based but instead derive from neonatal networks or facility-based cohorts, which may not reflect broader national or regional survival rates. High-quality, large-scale networks such as those from Europe, and Japan are overrepresented in the literature and contribute substantially to our pooled estimates. As such, the findings may overestimate survival in settings where outcomes for EPIs are less favourable and data less complete. There is a critical need for more inclusive, population-based data, particularly from low- and middle-income countries, to better inform global estimates and equity-focused strategies.

While we attempted to stratify data where available, many studies reported outcomes for wide gestational age ranges (e.g., 22–28 weeks), making it challenging to draw conclusions about specific gestational age subgroups. This is particularly relevant for infants born at 22–23 weeks, whose outcomes are heavily influenced by institutional and national policies regarding active treatment. Aggregating such diverse gestational ages can obscure important differences in survival and morbidity, potentially misrepresenting both the burden and progress in care. Where data allowed, we conducted subgroup analyses by individual gestational weeks to address this limitation, and we emphasize the need for future studies to report outcomes with greater gestational age granularity. Moreover, the majority of studies included to estimate survival without major morbidity rates of infants were from HICs. The lack of systemic data collection in LMICs, unlike high-income countries with established neonatal networks, may contribute to this limited reporting. Even where systems exist, reporting is often inconsistent. This underscores the need to strengthen surveillance systems to set benchmarks.

We also acknowledge the possibility that some relevant studies may have been missed despite our comprehensive search strategy. Limitations in indexing, non-English publications, and inconsistent reporting practices may have contributed to incomplete retrieval. Additionally, some included studies had very small sample sizes and/or a high risk of bias, which may affect the robustness and generalizability of the pooled estimates. Another key limitation is the uncertainty around denominator accuracy in many settings. In several countries or healthcare units, reliable data on live births and stillbirths are not consistently recorded, especially at the lowest gestational ages. This variability in data quality may influence survival estimates and introduces additional challenges in comparing outcomes across studies and regions.

Conclusion

In conclusion, while global data demonstrate encouraging trends in survival and morbidity outcomes among EPIs with increasing gestational age, profound disparities remain across income settings. Survival rates exceed 69% in high-income countries but fall to just over 32% in low-income countries, highlighting the inequitable distribution of neonatal care resources and outcomes. The limited, heterogeneous, and often incomplete data from low- and middle-income countries hinder robust comparisons and obscure the true impact of implemented interventions in these settings.

Moreover, differences in data quality, health system capacity, and population characteristics hinder direct comparisons across regions and time periods. These variations underscore the importance of developing context-specific strategies that align with local resources, cultural values, and ethical frameworks. There is a need for gestation-specific, population-level data particularly from low-and middle-income countries to inform equitable and evidence-based global neonatal care policies. Bridging these data gaps is essential for setting realistic, income-adjusted benchmarks and improving outcomes for the most vulnerable newborns worldwide.

Abbreviations

BPD	Bronchopulmonary dysplasia
CoE	Certainty of evidence
EPI	Extremely Preterm Infant
HIC	High-income countries
IVH	Intraventricular Haemorrhage
LMIC	Low-and-Middle-Income Countries
LIC	Low-income countries
MDGP	Millennium Developmental Goals Period
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
NOS	Newcastle–Ottawa Scale
ROP	Retinopathy of Prematurity
SDGP	Sustainable Developmental Goals Period

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Access to data and data analysis
The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' contributions
TG, KL, NH and AA were involved in title selection, gap identification, research question development and method writing. TG and HKK participated in data extraction and quality assessment. TG, KL, NH, AA and SJ were involved in the analysis, result writing, discussion, and manuscript preparation. All the authors have read and approved the last version of the manuscript.

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Declarations

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Competing interests
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