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# Risk Factors for Mortality in Neonates with a Congenital Heart Disease; A Systematic Review and Meta-Analysis

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## Abstract

**Background:** Congenital heart diseases (CHDs) are cardiovascular malformations related to atypical cardio-vascular development. The morbidity, mortality, and long-term outcomes of CHDs depend on the proper identification of neonates at a higher risk of death.

**Objectives:** This meta-analysis was conducted to reveal the potential pre-natal, peri-natal, and post-natal predictors of mortality among neonates with congenital heart diseases.

**Methods:** An extensive systematic literature review was performed until 28th August 2020. All clinical studies comparing the perinatal characteristics of survivors and non-survivors in neonates with CHDs were included. Studies reporting the potential predictors of mortality in neonates with CHDs were also included.

**Results:** This meta-analysis included 16 retrospective studies including 39232 neonates with CHDs. Patients were furtherly assorted into survivors and non-survivors groups, accounting for 29353 (78.65%) and 7967 (21.34%), respectively. The neonatal mortality rate was 23.7% (95CI%23.2% to 24.2%, p < 0.001) during the neonatal period. Caesarian deliveries (RR1.20; 95% 1.01, 1.44; P = 0.04), prematurity (RR4.38; 95%1.56, 12.32; P = 0.005), gestational age (20 - 31 weeks) (RR 3.96; 95%1.38, 11.39; P = 0.01), surgeons experience < 5 years (RR1.2; 95%1.09, 1.32; P = 0.0002) and cardiopulmonary bypass time (Mean Difference: MD-29.15 minutes; 95%-36.49, -21.80; P < 0.001) were statistically significant predictors of neonatal death from CHDs.

**Conclusion:** The risk factors for mortality in neonates with CHDs are prematurity, deliveries by caesarian delivery, low birth weight and neonatal necrotizing enterocolitis. Neonates with preoperative mechanical ventilation, prolonged cardiopulmonary bypass time, surgeries performed by less experienced surgeons, post-operative complications including acute kidney injury, thrombosis, or stroke after cardiac interventions were more likely to die from CHDs during the neonatal period.

***Keywords:*** *Neonatal; Mortality; Congenital Heart Diseases*

## Introduction

Congenital heart diseases (CHDs) are cardiovascular malformations related to atypical cardio-vascular development. The underlying aetiology of CHDs is complex, being associated with the concerted effects of environmental and genetic factors [1,2]. Currently, CHDs are

the most prevalent congenital anomalies, accounting for nearly 33% of all congenital birth defects. Due to the significant advancement in cardiovascular interventions, there was a substantial improvement in the survival rate in infants with CHD. The survival rate of infants with CHD improved from 67.4% to 82.5% in 1993 and 2005, respectively [3,4]. Before the era of cardiac surgery, nearly 30% of children with CHDs survived into adulthood, in contrast to 85% recently. This is because of the evolution in cardiac catheterization, cardiac surgery, anaesthetic techniques, and neonatal and pediatric intensive care support. However, CHDs remains a leading cause of death from birth defects, imposing a considerable disease burden on the health care systems [5,6].

Globally, CHDs caused more than 260000 infant-related deaths in 2017, being an autopsy finding in more than 85% of neonatal deaths [7,8]. Furthermore, CHDs are the main underlying aetiology of cardiac arrest during the first three decades of life, ranging from nearly 85% in the first two years to 20% in the second decade of life [9]. This figure was considerably high in low- and middle-income countries in which approximately 90% of the world's infants born with CHDs die [10]. Premature death might occur due to limited access to surgical treatment and subsequently due to cardiac and respiratory complications [11]. Therefore, adequate allocation of the health resources is mandatory to assort the suitable management of neonates with CHDs precisely. Understanding the potential risk factors of neonatal mortality from CHDs is important for healthcare providers and policymakers [12].

The morbidity, mortality, and long-term outcomes of CHDs depend on the proper identification of neonates with a higher risk of death. Recognising such factors will help healthcare providers specifically categorise and timely employ such neonates with CHDs in a suitable management plan [13]. This is associated with achieving functioning circulation, along with the restoration of normal cardiac anatomy [14]. Throughout the literature review, there is a demanding concern regarding the identification of the risk factors of mortality among neonates with CHDs [15,16]. On the contrary, the current evidence is still doubtful regarding the identification of such factors. Therefore, the current systematic review and meta-analysis was conducted to reveal the potential pre-natal, peri-natal, and post-natal predictors of mortality among neonates with congenital heart disease.

## Methods

This systematic review and meta-analysis was carried out following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [17] and the recommendations of Cochrane collaboration [18] (Supplementary table 1). The methodology of the study was documented in a protocol which was registered at http://www.crd.york.ac.uk/prospero/ (Registration number) CRD42021214928.

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | Page 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Page 2-3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | Page 4-5 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | Page 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Page 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Page 6 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | Page 5-6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Page 5-6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | Page 6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | Page6- 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | Page 6-7 |

| | | | |
|---|---|---|---|
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Page 7 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Page 7-8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | Page7- 8 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Page.7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Page 7-8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Page 8<br>Fig. 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Page 8-9<br>Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Page 8<br>Table 1 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Page 8<br>figs. 2-4, Sup. Figures.1 and 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Page 8-11<br>figs. 2-4, Sup. Figures.1 and 2 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Page 8<br>Table 1 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | figs. 2-4, Sup. Figures.1 and 2 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | Page 14 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | Page 16 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Page 17 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | N/A |

***Supplementary Table 1:*** *PRISMA 2009. Checklist.*

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097*

*For more information, visit: www.prisma-statement.org.*

### Data source

An extensive systematic literature review was implemented, up to 28 August 2020, using the following databases: PubMed, Google Scholar, Web of Science (ISI), Scopus, SIGLE, Virtual Health Library (VHL), NYAM, Clinical trials, Controlled Trials (mRCT), EMBASE and WHO International Clinical Trials Registry Platform (ICTRP). The following keywords were used in every possible combination; 'Mortality', 'Death', 'Survival', 'Neonates', 'Neonate', 'Neonatal', 'Newborn', 'Newborns', 'Congenital', 'Heart', and 'Cardiac'. A further manual search was performed to comprehend all retrieved studies' references to distinguish all additional conceivable articles that were not indexed. The cross-referencing method was carried out until no other relevant article was detected.

### Study selection

All clinical studies comparing the perinatal characteristics of survivors and non-survivors in neonates with CHDs were included. Studies that reported the potential predictors of mortality in neonates with CHDs were also included. There was no restriction on the patients' age, sex, race, ethnicity, language, publication dates or place. On the contrary, non-comparative studies or those that did not report the possible predictors of mortality were excluded. Furthermore, studies in which data was inaccessible, guidelines, review articles, animal studies, case reports, comments, letters, editorials, posters, and book chapters were excluded.

The relevant articles were exported to a Microsoft Excel sheet. The screening process of the title, abstract, and full text was performed independently by two reviewers to reveal the potentially relevant articles that met the inclusion criteria. Regular discussions dissolved the contradictions between the reviewers.

### Data extraction and quality assessment

The following data was extracted from the finally included articles; study characteristics (the title of the included study, the second name of the first author, year of publication, study design, study period, and study region), Pre-natal and maternal risk factors (Prenatal diagnosis of congenital heart disease, multiple gestations, maternal age, intrauterine growth retardation, single pregnancy, and maternal co-morbidities), peri-natal risk factors (Gestational age, birth weight, Apgar score, sex, race, and the mode of delivery) and post-natal risk factors (Type of cardiac anomaly, extra-cardiac anomalies, chromosomal abnormalities, pre-cardiac intervention, medications, pre-cardiac intervention mechanical ventilation, risk-adjusted classification for Congenital Heart Surgery (RACHS-1), cardiopulmonary bypass time, and cross-clamp time).

The quality of the observational studies was assessed using the National Institute of Health (NIH) quality assessment tool [19]. The studies were assorted, based on this quality assessment, into good, fair, and bad when the score was < 65%, 30 - 65%, > 30%, respectively. If the parameter was controlled, the domain was considered "Yes" and vice versa (Table 1).

### Statistical analysis

The prevalence of neonatal mortality was estimated by calculating the event rate and 95% confidence intervals (CIs) for each study succeeded by pooling the effect sizes of all studies to estimate the summary proportion with 95% CI. Weighted mean difference (WMD) or standardized mean difference (SMD) was used for analyzing the continuous variables. Mean and standard deviation (SD) were calculated from studies reported data using mean and range or median and range based on the equations exemplified by Hozo., *et al*. 2005 [20]. The risk ratio (RR) with 95% CI was used for analyzing dichotomous variables. The pooled summary of hazard ratios (HR) was computed by pooling the HR from all the relevant articles. The fixed-effect model was implemented when a fixed population effect size is assumed; otherwise, the random-effects model was used. Statistical heterogeneity was appreciated using Higgins $I^2$ statistic, at the value of > 50%, and the Cochrane Q ($Chi^2$ test), at the value of $p < 0.10$ [21]. To account for this heterogeneity, the random-effects model was

employed. Publication bias was assumed in the presence of an asymmetrical funnel plot and based on Egger's regression test (P-value < 0.10). Herein, the trim and fill method of Duvall and Tweedie was used [21]. Subgroup analysis was conducted based on the severity of depressive manifestations. Data analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive Meta-Analysis v2 software [22,23]. The significant difference was established at the value of $P < 0.05$.

## Results

An extensive systematic literature review revealed a total of 963 articles. After duplicates removal, 714 articles were included for the title and abstract screening. Whereas 24 articles were included for full-text screening, 17 articles were included for data extraction. Out of them, 14 articles were included for data extraction in addition to two articles identified through manual search, yielding a total of 16 articles for systematic review and meta-analysis. The process of the literature search is shown in figure 1.

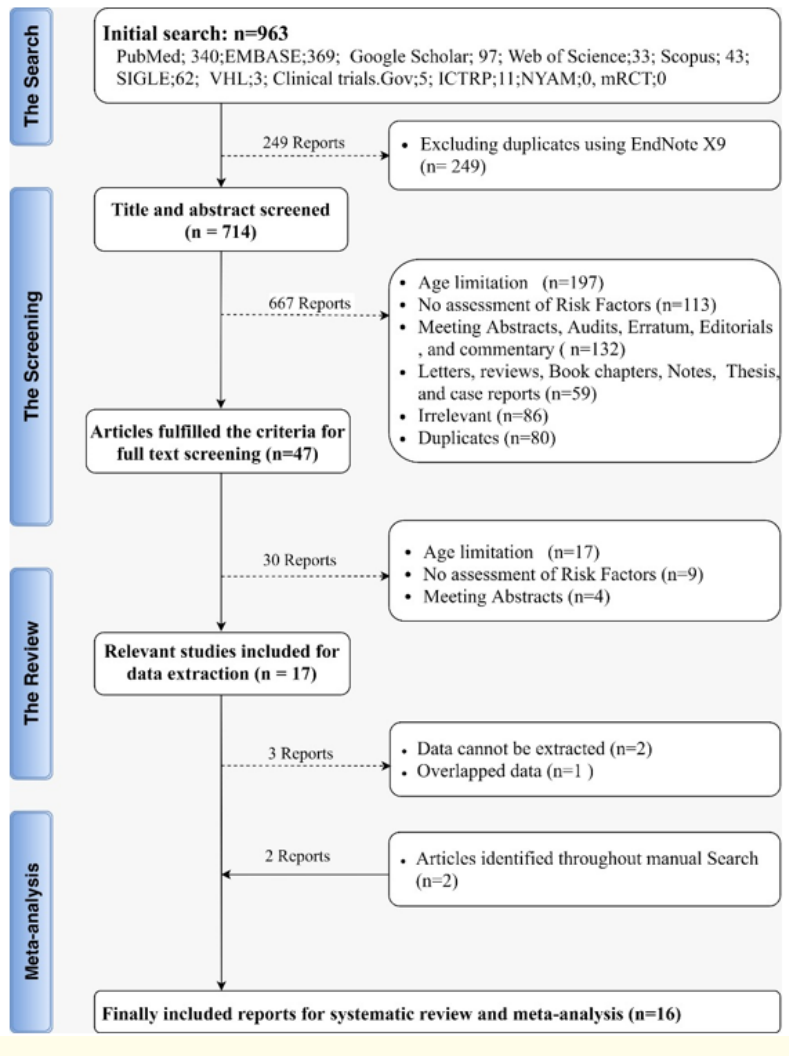



***Figure 1:*** *PRISMA Flow chart showing the process of the literature search, title, abstract, and full-text screening, systematic review, and meta-analysis.*

## Patient's demographic characteristics

This meta-analysis included 16 retrospective studies reporting the potential predictors of mortality among 39232 neonates with CHDs. There were 38414 (97.91%) patients from the USA and 126 (0.32%) cases from Korea. Out of 37320 neonates, patients were furtherly assorted into survivors and non-survivors groups, accounting for 29353 (78.65%) and 7967 (21.34%) cases, respectively. Of 34,749 patients, 11328 (41.11%) and 3925 (54.52%) males were among survivors and non-survivors groups, respectively. Prenatal diagnosis of CHDs was established among 1656 (39.40%) out of 4,202 cases. Associated extracardiac malformations were diagnosed among 584 neonates of 4,434 cases with a rate of 13.17%. Based on the NIH tool for quality assessment, all the included articles were considered of good quality (Table 1).

| Study ID | | Region | Study Design | Study Period Survivors Number | Sample Size | | Gender (Male) | | Prenatal Diagnosis | | Multiple Births | | Extra Cardiac Malformations | | Quality assessment | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Non-Survivors | Survivors | Non-Survivors | Survivors | Non-Survivors | Survivors | Non-Survivors | Survivors | Non-Survivors | | | |
| | | | | | Number | Number | Number | Number | Number | Number | Number | Number | Number | % | Decision | |
| 1 | Fixler., *et al*. 2014 | USA | Retrospective population-based registry | January 1, 1996, to December 31, 2007 | 1912 | | 1042 | | 311 | | NR | NR | 271 | | 81.81% | Good |
| 2 | Cavalcante., *et al*. 2016 | Brazil | Retrospective study | January 2003 to December 2014 | 236 | 118 | NR | NR | NR | NR | NR | NR | NR | NR | 72.72% | Good |
| 3 | Kucik., *et al*. 2014 | USA | Retrospective population-based registry study | 1999 to 2007 | 9853 | 1019 | NR | NR | NR | NR | NR | NR | NR | NR | 90.90% | Good |
| 4 | Shuhaiber., *et al*. 2012 | USA | Retrospective, | January 2002 to December 2008 | 56 | 56 | NR | NR | NR | NR | NR | NR | NR | NR | 81.81% | Good |
| 5 | Attar., *et al*. 2014 | USA | Retrospective study | 2002 and 2009 | 75 | 31 | 41 | 18 | NR | NR | 12 | 6 | 12 | 8 | 90.90% | Good |
| 6 | McKenzie., *et al*. 2017 | Australia | Retrospective cohort study | January 1, 2005, - December 31, 2014 | 60 | 50 | 29 | 29 | 42 | 39 | NR | NR | 16 | 10 | 90.90% | Good |
| 7 | ÜSTÜN., *et al*. 2014 | Turkey | Retrospective cohort study | September 2010 and January 2012 | 68 | 37 | 42 | 23 | 5 | 2 | NR | NR | 7 | 15 | 81.81% | Good |
| 8 | Yoon., *et al*. 2020 | Korea | Retrospective cohort study | January 2005 to December 2016 | 60 | 18 | 29 | 9 | NR | NR | NR | NR | 18 | 3 | 90.90% | Good |
| 9 | Cheng., *et al*. 2011 | USA | Retrospective cohort study | January 1, 2002, - December 31, 2008. | 143 | 31 | 28 | 7 | 78 | 20 | 30 | 5 | 23 | 5 | 90.90% | Good |
| 10 | Lynema., *et al*. 2016 | USA | Retrospective cohort study | October 2007 and November 2012 | 25 | 27 | 10 | 14 | 16 | 20 | 8 | 5 | 9 | 19 | 72.72% | Good |
| 11 | Lee., *et al*. 2016 | Korea | Retrospective cohort study | May 2007 and February 2014 | 33 | 15 | 18 | 9 | NR | NR | 2 | 0 | 7 | 5 | 90.90% | Good |
| 12 | Hong., *et al*. 2016 | China | Retrospective cohort study | January 2011 and December 2014 | 100 | 23 | 71 | 17 | NR | NR | NR | NR | NR | NR | 81.81% | Good |
| 13 | Mazwi., *et al*. 2013 | USA | Retrospective cohort study | January 1, 2002 to December 31, 2008 | 879 | 64 | 36 | 515 | 399 | 47 | 36 | 5 | 86 | 10 | 90.90% | Good |
| 14 | Atz., *et al*. 2010 | USA | Retrospective cohort study | May 2005 to July 2009 | 880 | 26 | NR | NR | 659 | 18 | | | 48 | 12 | 72.72% | Good |
| 15 | Ford., *et al*. 2016 | USA | Retrospective cohort study | 2001 through 2011 | 1832 | 2639 | 1,054 | 1551 | NR | NR | NR | NR | NR | NR | 81.81% | Good |
| 16 | Hamzah., *et al*. 2020 | USA | Retrospective population-based registry study | 2002 to 2016 | 15053 | 3813 | 9192 | 2184 | NR | NR | NR | NR | NR | NR | 72.72% | Good |
| **Abbreviations:** NR=Non-Reported | | | | | | | | | | | | | | | | |

***Table 1:*** *Demographic characteristics of the included studies.*

### Prevalence of neonatal mortality

A total of 15 articles, including 37324 patients, reported the proportion of neonatal mortality in patients with CHDs. In the random-effects model ($I^2$ = 99%, P < 0.001), the pooled analysis revealed a mortality rate of 23.7% (95-CI% 23.2% to 24.2%, p < 0.001) among neonates with CHDs during the neonatal period (Figure 2A).

### Prenatal and maternal predictors of mortality

### Race and Ethnicity

Three studies, including 23,443 patients, reported the impact of the non-Hispanic white race on the mortality risk. In the random-effects model ($I^2$ = 70%, P = 0.004), there was no statistically significant difference between survivors and non-survivors groups (RR 1; 95% 0.95, 1.05; P = 0.95). Similarly, there was no statistically significant impact of non-Hispanic black (RR 1.15; 95% 0.87, 1.51; P = 0.32) or Hispanic (RR 1.03; 95% 0.95, 1.10; P = 0.51) races on the risk of neonatal mortality (Supplementary figure 1A-1C).

### Maternal age

Two articles, including 12784 cases, reported the association between maternal age >36 years and neonatal mortality risk. In the random-effects model ($I^2$ = 77%, P = 0.004), there was no statistically significant association between maternal age and mortality (HR 1.10; 95% 0.42, 2.90; P = 0.85) (Supplementary figure 1D).

### Prenatal diagnosis and prenatal steroids

The impact of prenatal diagnosis on the subsequent neonatal mortality risk among patients with CHDs was evaluated within six studies including 2055 cases. Pooling the data revealed no statistically significant difference between survivors and non-survivors groups (RR 1.18; 95% 0.95, 1.47; P = 0.13). In this respect, there was no statistically significant impact of prenatal steroids on the neonatal mortality risk (RR 1.4; 95% 0.91, 2.15; P = 0.12) (Supplementary figure 1E and 1F).

### Multiple births

Five articles, including 1323 patients, reported the impact of multiple births on the survival of neonates with CHDs. In the random-effects model ($I^2$ = 1%, P = 0.4), there was no statistically significant difference between survivors and non-survivors groups (RR 1; 95% 0.64, 1.57; P = 0.99) (Supplementary figure 1G).

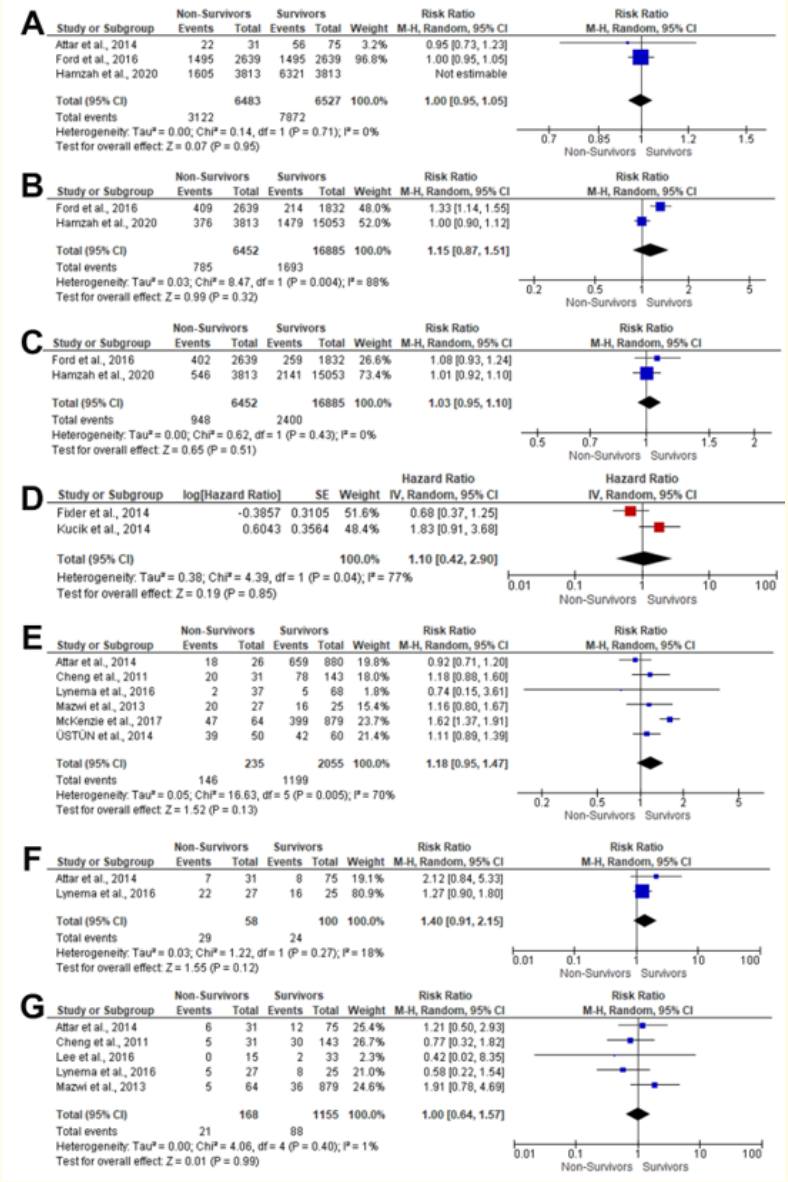
### Neonatal predictors of mortality

### Caesarian delivery

The impact of caesarian delivery on the mortality risk of 5,742 neonates with CHDs was reported in five articles. In the random-effects model ($I^2$ = 55%, P = 0.06), neonates delivered by cesarean delivery were 1.2 times more vulnerable to die from CHDs during the neonatal period (RR 1.20; 95% 1.01, 1.44; P = 0.04) (Figure 2B).

### Respiratory distress syndrome (RDS) at delivery

Two studies that included 1072 neonates with CHDs evaluated the association between RDS at delivery and neonatal mortality. In the random-effects model ($I^2$ = 86%, P = 0.007), neonates who developed RDS at delivery were 3.49 more likely to die from CHDs during the neonatal period (RR 3.49; 95% 1.29, 9.44; P = 0.01) (Figure 2C).




***Supplemntary Figure 1:*** *Forest plot of summary analysis of: (A) The risk ratio (RR) and 95CI% of the impact of non-Hispanic white race on the neonatal mortality risk in neonates with CHD. (B) The risk ratio (RR) and 95CI% of the impact of non-Hispanic black race on the neonatal mortality risk in neonates with CHD. (C) The risk ratio (RR) and 95CI% of the impact of Hispanic race on the neonatal mortality risk in neonates with CHD. (D) The Hazard ratio (HR) and 95CI% of the maternal age on the neonatal mortality risk in neonates with CHD. (E) The risk ratio (RR) and 95CI% of the impact of prenatal diagnosis of CHDs on the neonatal mortality risk. (F) The risk ratio (RR) and 95CI% of the impact of prenatal steroids on the neonatal mortality risk in neonates with CHD. (G) The risk ratio (RR) and 95CI% of the impact of multiple births on the neonatal mortality risk in neonates with CHD. Size of the red or blue squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).*

### Gestational age

Three articles that included 304 neonates with CHDs reported the mortality risk in patients with gestational age (20 - 31 weeks). In the random-effects model ($I^2$ = 62%, P = 0.07), neonates with a gestational age of 20-31 weeks were 3.96 times more susceptible to die of CHDs throughout the neonatal period (RR 3.96; 95% 1.38, 11.39; P = 0.01) (Figure 2D).

### Prematurity

The risk of neonatal mortality from CHDs among premature neonates was reported within two studies included 217 cases. The pooled analysis revealed that premature neonates with CHDs were 4.38 times more susceptible to die from CHDs in the first 28 days of life (RR 4.38; 95% 1.56, 12.32; P = 0.005) (Figure 2E).

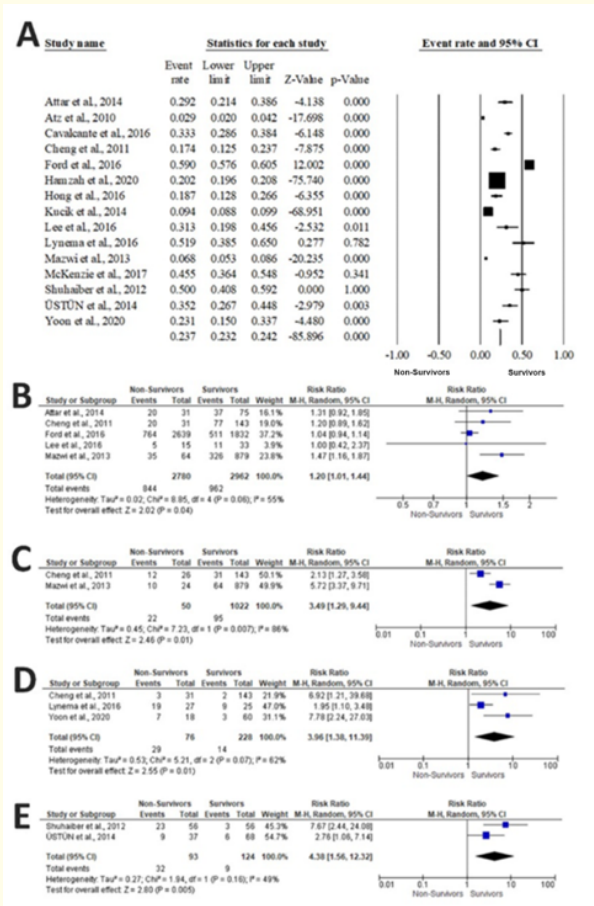



***Figure 2:*** *Forest plot of summary analysis of (A) the event rate and 95% CIs of the prevalence of neonatal mortality from CHDs. (B) The risk ratio (RR) and 95CI% of the impact of caesarian delivery on the neonatal mortality risk in neonates with CHD. (C) The risk ratio (RR) and 95CI% of the impact of respiratory distress syndrome at delivery on the neonatal mortality risk in neonates with CHD. (D) The risk ratio (RR) and 95CI% of gestational age on the neonatal mortality risk in neonates with CHD. (E) The risk ratio (RR) and 95CI% of the impact of prematurity on the neonatal mortality risk in neonates with CHD. Size of the black or blue squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).*

### Birth weight

The association between birth weight < 2.5kg and neonatal mortality in neonates with CHDS was reported in five articles, including 12052 participants. In the random-effects model ($I^2$ = 91%, P < 0.0001), neonates who weighed less than 2.5 kg at delivery were 2.67 times more vulnerable to die from CHDs in the neonatal period (RR 2.67; 95% 1.04, 6.84; P = 0.04) (Figure 3A).

### Extracardiac malformations and disorders

Nine studies, including 2,522 neonates with CHDs, reported the impact of extracardiac malformations on the neonatal mortality risk. In the random-effects model ($I^2$ = 85%, P < 0.0001), there was no statistically significant difference between survivors and non-survivors groups (RR 1.75; 95% 0.93, 3.30; P = 0.08) (Supplementary figure 2A).

Two articles reported the impact of necrotizing enterocolitis on neonatal mortality risk in patients with CHDs. Patients with NEC were 4.67 times more vulnerable to die of CHDs in the neonatal period (RR 4.67; 95% 1.22, 17.89; P = 0.02) (Figure 3B).

### Pre-operative predictors of mortality

### RACHS risk category

Two studies including 4,583 neonates reported the role of RACHS risk category in predicting mortality from CHDs. In the random-effects model ($I^2$ = 66%, P = 0.03), patients with RACHS risk category 4 were 1.53 times more susceptible to die of CHDs (RR 1.53; 95% 1.08, 2.16; P = 0.02) (Figure 3C).

There was no statistically significant difference between survivors and non-survivors groups (RR 1.34; 95% 0.63, 2.86; P = 0.45) regarding RACHS risk category 1. In this concern, there was no statistically significant difference between both groups regarding RACHS risk category 2 (RR 0.7; 95% 0.25, 1.95; P = 0.49), RACHS risk category 3 (RR 1.25; 95% 0.88, 1.77; P = 0.22) and RACHSS risk category ≥ 5 (RR 1.68; 95% 0.86, 3.31; P = 0.13) (Supplementary figure 2B-2E).

### Preoperative mechanical ventilation

A total of 1332 neonates with CHDs within four studies required mechanical ventilation preoperatively. In the random-effects model ($I^2$ = 0%, P = 0.42), these neonates were 1.44 times more vulnerable to die with CHDs in the neonatal period (RR 1.44; 95% 1.29, 1.61; P < 0.001) (Figure 3D).

### Surgeon experience < 5 years

Two studies that included 4583 neonates with CHDs evaluated the impact of surgeons' experience on neonatal mortality. The pooled analysis revealed that neonates with CHDs operated by surgeons with experience < 5 years were 1.2 times more likely to die through the neonatal period (RR 1.69; 95% 1.44, 1.99; P < 0.001) (Figure 3E).

### Biventricular repair

Two articles included 4583 neonates with CHDs assessed the association between biventricular repair and neonatal mortality. The pooled analysis revealed that patients who received biventricular repair were more susceptible to die of CHDs in the neonatal period (RR 0.92; 95% 0.87, 0.98; P = 0.004) (Figure 3F).

### Preintervention PGE1

Two studies that included 252 neonates with CHDs reported the mean levels of PGE1 preoperatively. In the random-effects model ($I^2$ = 0%, P = 0.42), there was a statistically significant higher mean of PGE1 among survivors (MD -36.79; 95% -66.84, -6.75; P = 0.02), relative to non-survivors (Figure 3G).

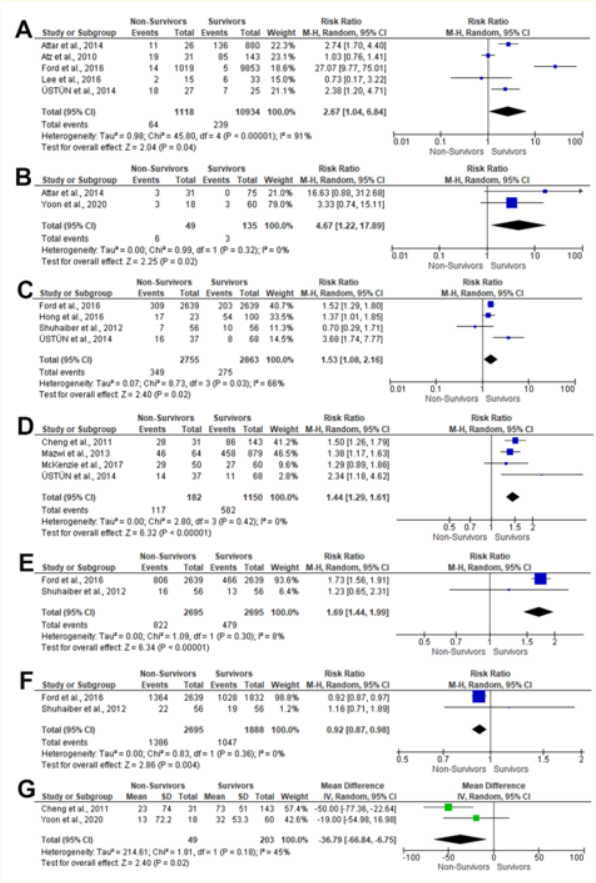
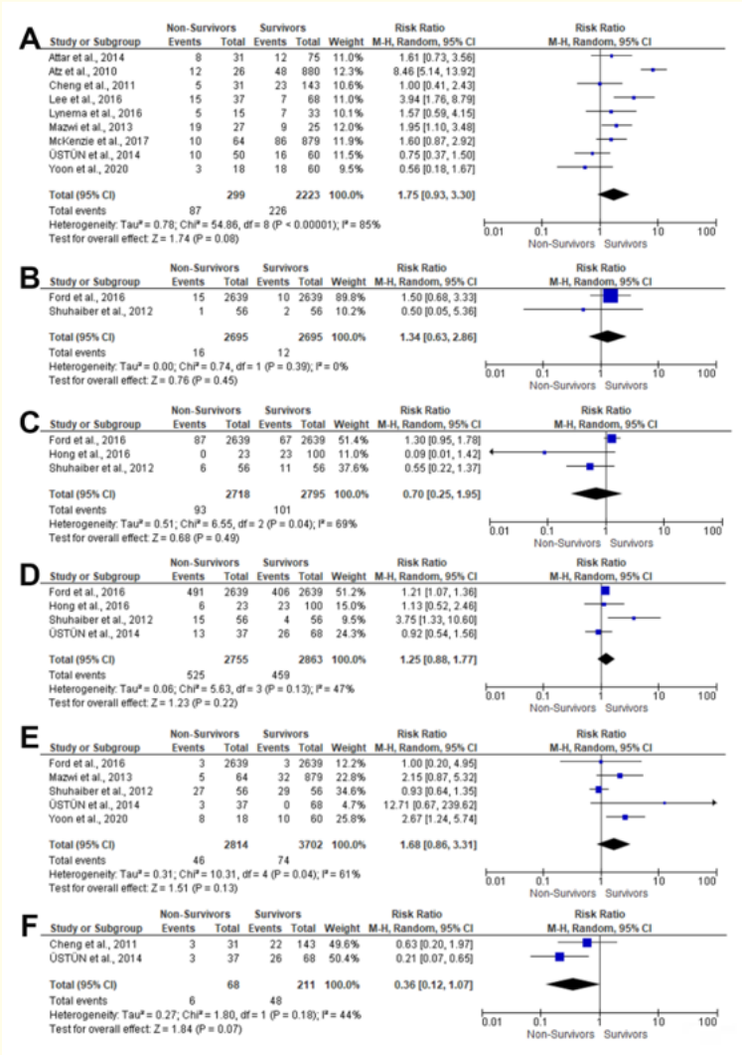



***Figure 3:*** *Forest plot of summary analysis of: (A) The risk ratio (RR) and 95CI% of the impact of birth weight<2.5 kg on the neonatal mortality risk in neonates with CHD. (B) The risk ratio (RR) and 95CI% of the impact of necrotizing enterocolitis on the neonatal mortality risk in neonates with CHD. (C) The risk ratio (RR) and 95CI% of the impact of RACHS risk category 4 on the neonatal mortality risk in neonates with CHD (D) The risk ratio (RR) and 95CI% of the impact of Preoperative mechanical ventilation on the neonatal mortality risk in neonates with CHD. (E) The risk ratio (RR) and 95CI% of surgeons' experience < 5 years on the neonatal mortality risk in neonates with CHD (F) The risk ratio (RR) and 95CI% of the impact of biventricular repair on the neonatal mortality risk in neonates with CHD (G) The mean difference (MD) and 95CI% of preintervention PGE1 between survivors and non-survivors neonates with CHD. Size of the green or blue squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).*

## Intra-operative and post-operative predictors of mortality

### Initial cardiac catheterization

The impact of initial cardiac catheterization on the subsequent neonatal mortality risk in neonates with CHDs was evaluated among 289 patients within two studies. There was no statistically significant difference between survivors and non-survivors groups (RR 0.36; 95% 0.12, 1.07; P = 0.07) (Supplementary figure 2F).




***Supplemntary Figure 2:*** *Forest plot of summary analysis of the risk ratio (RR) and 95CI% of the impact of: (A) The extracardiac malformations on the neonatal mortality risk in neonates with CHD. (B) RACHS-1 risk category on the neonatal mortality risk in neonates with CHD. (C) RACHS-2 risk category on the neonatal mortality risk in neonates with CHD. (D) RACHS-3 risk category on the neonatal mortality risk in neonates with CHD. (E) RACHS ≥ 5 risk category on the neonatal mortality risk in neonates with CHD. (F) Initial cardiac catheterization on the neonatal mortality risk in neonates with CHD. Size of blue squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).*

### Cardiopulmonary bypass time (min)

The difference in cardiopulmonary bypass time between survivors and non-survivors groups was estimated among 1176 within three studies. In the random-effects model ($I^2$ = 35%, P = 0.22), survivors had a statistically significant prolonged cardiopulmonary bypass time, relative to non-survivors (MD 29.15 minutes; 95% 21.80, 36.49; P < 0.001) (Figure 4A).

### Cross-clamp time (min)

Two studies, including 233 neonates with CHDs, assessed the difference in cross-clamp time between survivors and non-survivors groups. In the random-effects model ($I^2$ = 35%, P = 0.22), survivors had a statistically significant shorter cross-clamp time, in contrast to non-survivors (MD 7.81 minutes; 95% 2.60, 13.01; P = 0.003) (Figure 4B).

### Post-operative complications

Three studies reported the impact of postcardiac surgery acute kidney injury on the neonatal mortality of 4686 neonates with CHDs. Neonates who developed AKI were 2.62 times more likely to die after surgery (RR 2.62; 95% 1.09, 6.29; P = 0.03). Similarly, patients who developed dysrhythmia (RR 2.6; 95% 2.22, 3.05; P < 0.0001) and thrombotic events (RR 3.39; 95% 1.87, 6.15; P < 0.001) after surgery were 1.81 and 3.39 times more likely to die within the neonatal period (Figure 4C-4E).

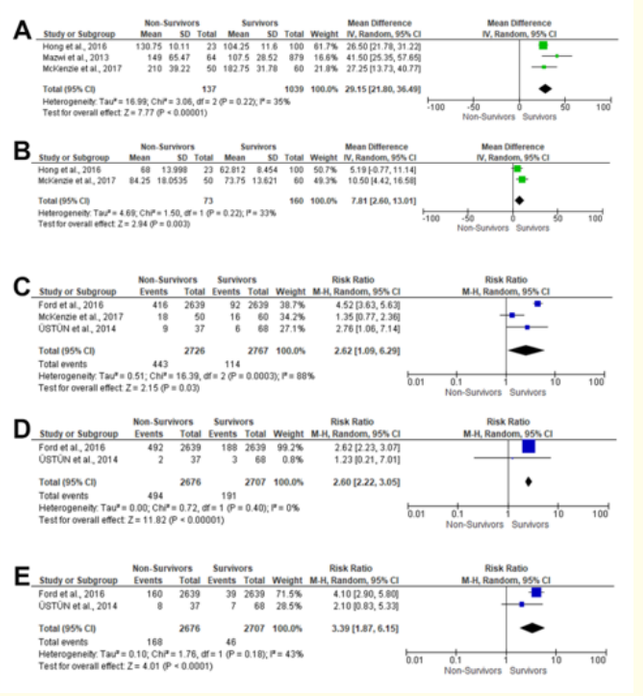



***Figure 4:*** *Forest plot of summary analysis of: (A) The Mean difference (MD) and 95CI% of cardiopulmonary bypass time between survivors and non-survivors groups. (B) The Mean difference (MD) and 95CI% of cross-clamp time between survivors and non-survivors groups. (C) The risk ratio (RR) and 95CI% of the impact of postcardiac surgery acute kidney injury on the neonatal mortality risk in neonates with CHD. (D) The risk ratio (RR) and 95CI% of the impact of postcardiac surgery dysrhythmia on the neonatal mortality risk in neonates with CHD. (E) The risk ratio (RR) and 95CI% of the impact of postcardiac surgery thrombotic events on the neonatal mortality risk in neonates with CHD. Size of the green or blue squares is proportional to the statistical weight of each trial. The grey diamond represents the pooled point estimate. The positioning of both diamonds and squares (along with 95% CIs) beyond the vertical line (unit value) suggests a significant outcome (IV = inverse variance).*

## Discussion

Congenital heart diseases are a recognised leading cause of neonatal mortality [24]. The timely identification of neonates with CHDs who are at a higher risk of rapid health deterioration is of great importance. There were continuous efforts to evaluate the potential neonatal mortality predictors of CHDs. These efforts although scanty are raising awareness in healthcare providers to gather the available evidence in a well-structured conclusive report [25,26]. Therefore, this systematic review and meta-analysis was conducted to assess the potential neonatal predictors of mortality among 39232 neonates with CHDs from six different nations, representing the largest cohort of literature.

In the current meta-analysis, premature neonates with CHDs, newborns delivered by caesarian delivery, babies who developed RDS, neonates with gestational age (20 - 31 weeks), patients weighed less than 2.5 kg, or those who had NEC were at a higher risk of death from CHDs during the neonatal period. Contrary to these findings, prenatal diagnosis, prenatal steroids, or the presence of extracardiac malformations had a statistically significant impact on neonatal mortality. Preterm neonates with LBW had severe growth restriction, neurodevelopmental delay, and additional risk for co-morbidities. This included a higher incidence of NEC, RDS, and neonatal sepsis. These factors further complicate the existing circulatory dysfunction, increase the cardiac interventions' complexity, and ultimately decrease the neonatal survival rates [27,28]. The small size of the cardiovascular structures and the immature vital organs have a significant life-threatening risk during cardiac procedures [29].

In contrast to the findings of this meta-analysis, Li., *et al*. 2016 [30] reported a significant impact of prenatal diagnosis of transposition of great arteries on the preoperative and post-operative mortality. They reported that prenatal diagnosis of such cases allowed optimal perinatal care, as well as perioperative management. This includes delivery at a qualified unit, providing immediate mechanical ventilation, prostaglandins administration, or balloon atrio-septostomy if necessary [31,32]. The contradictory findings between the current systematic review results and Li., *et al*. 2016 meta-analysis might be attributed to the difference in comparative arms in both studies. In Li., *et al*. 2016 study, they compared the outcomes of prenatally diagnosed to postnatally diagnosed CHDs [30].

Early cardiac interventions shall prevent further cardiac or neurological decompensations due to hypoxia and impaired hemodynamics associated with CHDs. However, neonates with CHDs might face more surgical challenges when cardiac interventions are performed earlier. Prenatal diagnosis of CHDs may offer valuable information for clinical decision-making, increasing the chances of attaining better perioperative outcomes [33,34]. Whereas delayed cardiac intervention may allow enough time for adequate growth and maturation of the cardiovascular system and improve surgical outcomes. Some authors suggest a comparable survival outcome in premature neonates subjected to timely cardiac interventions [35,36]. The balance between the risk of earlier cardiac interventions and the potential benefits of early restoration of the heart's normal anatomy and functions require further studies to confront this uncertainty.

Preoperatively, the risk-adjusted classification for Congenital Heart Surgery (RACHS-1 risk category) failed to predict the neonatal mortality risk in neonates seeking cardiac interventions. Despite being a feasible tool, RACHS risk category does not mitigate structural and individual factors related to heart procedures that may affect neonatal mortality. This includes the complexity and the variety of the cardiac interventions, as well as the associated neonatal comorbidities such as infection, renal dysfunction, and portal hypertension. These factors have a great influence on the survival outcomes in patients with CHDs [37-39]. To overcome these limitations, Mattos., *et al*. 2006 [38] proposed a clinical surgical score to evaluate the risk of in-hospital mortality, putting into consideration the nutritional status, age, cardiopulmonary bypass time, and other clinical factors of neonates with CHDs.

In this meta-analysis, neonates who received preoperative mechanical ventilation, patients with lower preoperative PGE1 levels, those operated by surgeons with experiences of < 5 years in cardiac surgeries or newborns subjected to biventricular repair were more likely to die of CHDs during the neonatal period. Patients with prolonged cardiopulmonary bypass time or shorter cross-clamp time were at

a higher risk to die from CHDs. Preoperative mechanical ventilation is indicative of decompensated cardiopulmonary status. Prolonged preoperative mechanical ventilation might lead to alveolar collapse, poor lung perfusion, and reduced pulmonary vascular resistance. This in turn leads to lung injury, systemic inflammation and RDS [40,41]. Prolonged cardiopulmonary bypass time is associated with immunoparesis, inflammation, and disturbances in the coagulation system. It may also compromise the lung surfactant, leading to respiratory dysfunction in premature lungs [42,43].

Neonates receiving cardiac interventions have a limited physiological reserve, making them more vulnerable to decompensate the intense hemodynamic instability associated with cardiac surgeries. In this respect, the anatomical diversity, circulatory dysfunctions, comorbidities, and technical challenges render cardiac interventions with complicated approaches, requiring higher surgical experience [36,44].

This is the first study gathering the rapidly emerging controversial evidence regarding the potential predictors of mortality among neonates with CHDs. On the contrary, some limitations should be put into consideration while interpreting the yielded evidence. Most of the included articles were of the retrospective design, revealing a potential risk of selection bias. Additionally, there was significant heterogeneity between the included studies. This heterogeneity might evolve due to demographic characteristics, assessment methods, surgical techniques, and follow-up periods.

## Conclusion

The risk factors for mortality in neonates with CHDs are prematurity, deliveries by caesarian delivery, low birth weight and neonatal necrotizing enterocolitis. Neonates with preoperative mechanical ventilation, prolonged cardiopulmonary bypass time, surgeries performed by less experienced surgeons, postoperative complications including acute kidney injury, thrombosis, or stroke after cardiac interventions were more likely to die from CHDs during the neonatal period. The integration of these findings in healthcare protocols will help the health care providers identify patients with a higher risk of mortality and thereby enhance the outcomes of CHDs by stratifying these patients to the most appropriate and effective treatment in a timely fashion. However, further studies should be conducted to overcome the limitations of the current meta-analysis.

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