Congenital heart disease associated with congenital diaphragmatic hernia: A systematic review on incidence, prenatal diagnosis, management, and outcome

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Purpose: The purpose of this study was to evaluate the impact of congenital heart disease (CHD) on infants with congenital diaphragmatic hernia (CDH).
Methods: Using a defined search strategy (PubMed, Cochrane, Embase, Web of Science MeSH headings), we searched studies reporting the incidence, management, and outcome of CDH infants born with associated CHD.
Results: Of 6410 abstracts, 117 met criteria. Overall, out of 28,974 babies with CDH, 4427 (15%) had CHD, of which 42% were critical. CDH repair was performed in a lower proportion of infants with CHD (72%) than in those without (85%; p b 0.0001). Compared to CDH babies without CHD, those born with a cardiac lesion were more likely to have a patch repair (45% vs. 30%; p b 0.01) and less likely to undergo minimally invasive surgery (5% vs. 17%; p b 0.0001). CDH babies with CHD had a lower survival rate than those without CHD (52 vs. 73%; p b 0.001). Survival was even lower (32%) in babies with critical CHD.
Conclusion: CHD has a strong impact on the management and outcome of infants with CDH. The combination of CDH and CHD results in lower survival than those without CHD or an isolated cardiac defect. Further studies are needed to address some specific aspects of the management of this fragile CDH cohort.
Type of study: Systematic review and meta-analysis.
Level of evidence: Level III.

Congenital diaphragmatic hernia (CDH) is a severe birth defect, which is still burdened by high morbidity and mortality rates [1–3]. The majority of infants with CDH suffer from a combination of pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction [4–6]. Moreover, in almost half of the cases, CDH occurs in associationwith other congenital anomalies, the most frequent of which are cardiac lesions [7–13]. Congenital heart disease (CHD) in patients with CDH comprises a broad spectrum of cardiac anomalies that range from simple remnants of fetal circulation, such as a patent ductus arteriosus (PDA), to complex lethal heart diseases [14]. A way to assess the severity of CHD is by evaluating the need and/or urgency of cardiac intervention. According to the classification of the United States National Library of Medicine, lesions that require urgent intervention in the early neonatal period to prevent death are considered critical [15]. Some of the most complex aspects for the management of patients with CDH and associated CHD are the timing and prioritization of the diaphragmatic and cardiac repairs, especially in infants with a critical lesion. However, only a few studies have investigated this aspect. Likewise, several studies have focused on this fragile population of patients with CDH and CHD and have mainly reported increased mortality and morbidity rates compared to babies without CHD [7,16–23]. However, aspects of the management such as the accuracy of prenatal diagnosis, the use of extracorporeal membrane oxygenation (ECMO) and the role of fetoscopic endoluminal tracheal occlusion (FETO) remain controversial.

Herein, we systematically reviewed the literature to determine the incidence of CHD in CDH patients, and to evaluate the management and the impact of CHD on the outcome of these infants.

1. Material and methods

1.1. Data sources and study selection

This study was registered on PROSPERO — international prospective register of systematic reviews (registration number: CRD42018102679) [24]. The systematic review was drafted according to the Preferred

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Table 1
Inclusion criteria for the systematic review.

Publication	
Language	English
Date	Until June 2018
Subject	Human studies
Study type	Retrospective
	Prospective
	Case control
	Cohort
Excluded	Case reports
	Case series
	Letters
	Editorials
	Gray Literature
Keywords	Congenital diaphragmatic hernia
	Cardiac
	Heart

Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [25]. A systematic review of the literature was conducted using a defined search strategy (Table 1). Two investigators (LM and GL) independently searched scientific databases (PubMed, Medline, Cochrane Collaboration, Embase and Web of Science) using a combination of keywords. MeSH headings and terms used were "congenital diaphragmatic hernia" and "cardiac" or "heart". Reference lists were searched to identify relevant cross-references. Case reports, opinion articles and animal studies were excluded from the review. All gray literature publications (i.e. reports, theses, conference proceedings, bibliographies, commercial documentations, and official documents not published commercially) were excluded. Articles irrelevant to our search or articles reporting cohorts of CDH patients, but excluding selected CHD were excluded. The full text of potentially eligible studies was retrieved and independently assessed for eligibility by the two investigators.

The main outcome measures of this study were incidence, prenatal diagnosis, management, survival and morbidity of CHD in infants with CDH.

1.1.1. Incidence

The incidence of CHD was analyzed in all CDH patients (*overall incidence*), as well as in live-births, still-births, and pregnancy terminations, whenever explicitly reported. Moreover, we reported the incidence of CHD in patients with bilateral CDH as well as in late-presenting CDH (defined as diagnosed at N 30 days of life). To avoid data duplication owing to overlapping patient populations reported in multiple articles based on the same databases, we decided to include the article with the largest cohort of patients.

1.1.2. Prenatal diagnosis

We analyzed the rate of prenatal diagnosis of CHD at the fetal echocardiogram in fetuses with CDH.

1.1.3. Management

We analyzed the impact of CHD in infants with CDH undergoing diaphragmatic repair, cardiac intervention, use of ECMO, and use of FETO.

1.1.4. Survival

We included only studies reporting the survival rate of babies born with CDH, whose cardiac defect was clearly described. To distinguish CHD cases, we used a classification based on the physiology of the lesion: single ventricle lesions, ductal-dependent pulmonary circulation, ductal-dependent systemic circulation, total mixing lesions, nonmixing lesions and shunts. The first five groups were considered critical, and shunts were considered noncritical.

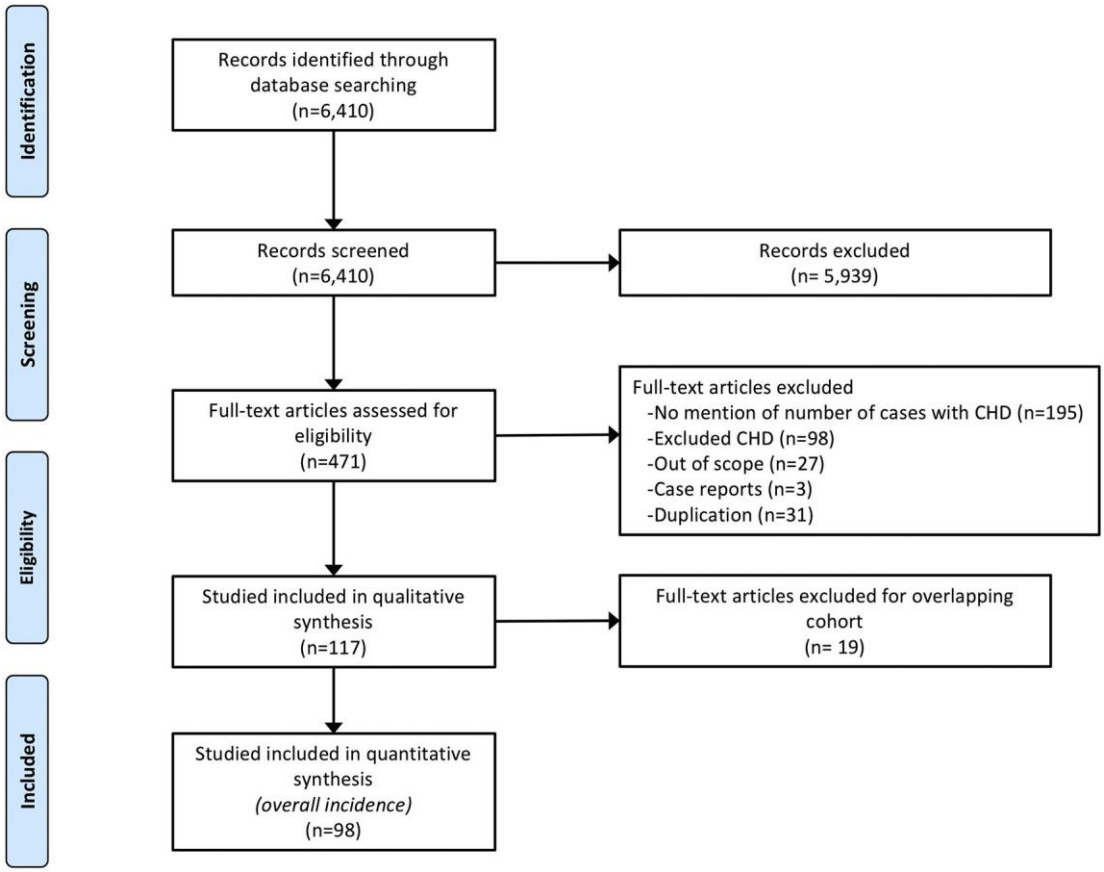

Fig. 1. Diagram of workflow in the systematic review according (PRISMA flowchart).

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1.1.5. Morbidity

We included studies that reported cardiac, pulmonary, and neurological outcomes in CDH patients with CHD compared to those without.

1.2. Statistical analysis

Categorical variable frequencies were compared using Pearson's chi-square test or the two-tailed Fisher exact probability test, as appropriate.

Meta-analysis of comparative studies was conducted with RevMan 5.3 [26], using the random-effects model to produce risk ratio (RR) for categorical variables, along with 95% confidence intervals (CI). A p-value b0.05 was considered statistically significant.

1.3. Quality assessment

Risk of bias for individual studies was assessed using the methodological index for nonrandomized studies (MINORS) [27]. Differences between the two reviewers (LM and GL) were resolved through consensus and discussion with a third author (AZ). The total score for this 12-item instrument ranges from 0 to 24 points with a validated "gold standard" cut-off of 19.8.

For each outcome, we graded the quality of evidence as high, moderate, low and very low, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [28]. The quality of evidence was rated down in the presence of risk of bias, inconsistency, indirectness, imprecision and publication bias. For assessment of risk of bias in observational studies, we used the MINORS instrument. Inconsistency was determined according to heterogeneity. We produced I^2 values to assess heterogeneity. I^2 values of 0–40, 30–60, 50–90, and 75–100% were considered as low, moderate, substantial, and considerable heterogeneity, respectively. Imprecision was assessed using optimal information size (OIS), which was based on 25% relative risk reduction, 0.05 of α error and 0.20 of β error [29]. Publication bias was assessed using funnel plots.

2. Results

2.1. Study selection and characteristics

The search initially yielded 6410 articles screened for potentially relevant studies. Based on title and abstract, 5939 were excluded. Four hundred and seventy-one full text articles were evaluated for inclusion criteria (Fig. 1). One hundred and forty-eight articles met the inclusion criteria. Thirty-one studies were excluded because of duplication. All studies were retrospective; there were no prospective or randomized controlled trials. After full-text review, 117 articles were the subject of this review.

The studies were conducted from 1960 to 2016, and published between 1975 and 2018. Most studies were conducted in Europe (35%) or North America (35%), 17% were conducted in Asia, 4% in Australia, 2% in South America. Six studies were from intercontinental databases (at least two continents) [17,30–34].

2.2. Incidence

After excluding 19 articles because of overlapping cohorts, ninety-eight articles (n = 28,974 CDH patients) met the inclusion criteria [7,14,17,18,20,21,23,30–121]. Overall, out of 28,974 babies with CDH, 4427 (15%; range 1–58%) had CHD (Table 2).

Out of the 51 articles included, the incidence of CHD in live-births CDH infants was 17% (17,534 CDH infants, range 3–54%) (Table 2). We found a similar incidence of CHD in CDH patients regardless if they were enrolled in a multicenter study (17%, 2276/13,675; 12 studies [4,17,20,32,34,85,93,97,110,111,114,119]) or if they were from a single-institution study (17%, 651/3859; 39 studies [7,14,18,21,23,35–50,57,73,75,77,78,81–84,89,92,98,99,104,105,108,112,113]).

Four studies focused on the association of CHD and CDH in still-births and pregnancy terminations (Table 2) [18,23,73,83]. From these studies, we calculated an incidence of 28% in still-births (5/18, range 0–57%) and 27% in pregnancy terminations (30/112, range 20–50%).

Table 2
Studies included in analysis for incidence of CHD in CDH.

Reference	Study period	Incidence	CDH	CDH and CHD
Overall (N = 98)	1962–2018	15%	28,974	4427
[7,14,17,18,20,21,23,30–121]				
Live-births				
Greenwood et al. 1976 [35]	1962–1973	23%	48	11
Puri et al. 1984 [36]	1973–1982	16%	25	4
Nakayama et al. 1985 [37]	1979–1982	30%	20	6
Mallik et al. 1995 [38]	1978–1994	17%	52	9
Ssemakula et al. 1997 [39]	1985–1996	12%	111	13
Reyes et al. 1998 [40]	1993–1996	13%	24	3
Losty et al. 1999 [41]	1970–1992	9%	301	26
Khawahur et al. 1999 [42]	1989–1996	21%	33	7
Suda et al. 2000 [43]	1992–1996	17%	41	7
CDH Study Group 2001 [32]	1995–1999	16%	966	156
Cohen et al. 2002 [23]	1996–2000	18%	145	26
Dott et al. 2003 [44]	1968–1999	13%	230	30
Rozmiarek et al. 2004 [45]	1991–2002	37%	111	41
[illegible]	1995–200	17%	145	25
Fumino et al. 2005 [47]	1981–2004	15%	46	7
Rygl et al. 2006 [50]	1996–2004	7%	104	7
Okawada et al. 2006 [48]	1979–2005	21%	100	21
Harmath et al. 2006 [121]	1990–2005	29%	106	31
Levison et al. 2006 [49]	1992–2001	15%	200	30
Migliazza et al. 2007 [75]	1994–2005	11%	111	12
Lin et al. 2007 [14]	1972–2002	11%	203	23
Beck et al. 2008 [73]	1995–2004	16%	19	3
Fisher et al. 2008 [77]	1990–2006	13%	267	34
Vivante et al. 2008 [78]	1985–2007	12%	68	8
Olgun et al. 2009 [81]	1998–2007	8%	25	2
Chao et al. 2010 [82]	1987–2008	54%	24	13
Chang et al. 2010 [84]	1987–2007	17%	85	14
Vogel et al. 2010 [83]	1998–2008	24%	85	20
Aly et al. 2010 [85]	1997–2004	22%	2140	481
Van den Hout et al. 2011 [87]	2006–2009	17%	167	28
Antonoff et al. 2011 [89]	2002–2011	13%	94	12
Benjamin et al. 2013 [98]	2001–2005	16%	43	7
Gray et al. 2013 [21]	1997–2011	19%	216	40
Jawaid et al. 2013 [92]	1990–2010	27%	118	32
Edmonds et al. 2013 [99]	1987–2010	8%	52	4
[illegible]	2005–2010	9%	348	33
Takahashi et al. 2013 [20]	2006–2010	18%	614	108
Menon et al. 2013 [17]	2000–2010	18%	4268	757
Wynn et al. 2013 [97]	2005–2012	21%	220	47
Hidaka et al. 2015 [104]	2005–2013	19%	63	12
Akinkuoto et al. 2016 [7]	2004–2014	30%	189	56
Garcia et al. 2016 [105]	2001–2013	16%	81	13
Kalanj et al. 2016 [108]	2005–2014	7%	42	3
Hung et al. 2016 [112]	2007–2014	3%	39	1
Murthy et al. 2016 [110]	2010–2014	14%	677	94
Hagadorn et al. 2015 [110]	2003–2012	13%	3123	393
Grizelj et al. 2017 [34]	1991–2016	13%	228	29
Kadir et al. 2017 [113]	1995–2016	19%	113	21
Long et al. 2018 [114]	2009–2010	9%	219	20
Bent et al. 2018 [119]	2007–2012	18%	705	130
Hautala et al. 2018 [18]	2002–2011	21%	80	17
Total (N = 51)		17%	17,534	2927
Still-births				
Cohen et al. 2002 [23]	1996–2002	10%	10	1
Vogel et al. 2010 [83]	1998–2008	0%	1	0
Hautala et al. 2018 [18]	2002–2011	57%	7	4
Total (N = 3)		28%	18	5
Pregnancy terminations				
Cohen et al. 2002 [23]	1996–2002	21%	19	4
Beck et al. 2008 [73]	1995–2004	50%	10	5
Vogel et al. 2010 [83]	1998–2008	20%	25	5
Hautala et al. 2018 [18]	2002–2011	28%	58	16
Total (N = 4)		27%	112	30

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Table 3
Incidence of CHD diagnosed prenatally in fetuses with CDH.

	Incidence
Fogel et al. 1991 [56]	18% (2/11)
Sharland et al. 1992 [52]	16% (9/55)
Manni et al. 1994 [130]	32% (9/28)
Geary et al. 1998 [55]	9% (3/34)
Witters et al. 2001 [54]	5% (2/42)
Gallot et al. 2006 [53]	13% (3/24)
Vogel et al. 2010 [83]	23% (25/111)
Lee et al. 2013 [96]	27% (6/22)
Mesas Burgos et al. 2016 [107]	4% (2/53)
Oh et al. 2016 [106]	19% (13/69)
Sperling et al. 2018 [115]	15% (27/184)
Total (N = 11)	16% (101/633)

The incidence of CHD in CDH was higher in these latter two groups than in live-births (p = 0.003).

When investigating the incidence of CHD in bilateral CDH, we found two articles from the CDH Study Group, published in 2003 and in 2017 [122,123]. These studies reported an incidence of CHD in CDH patients of 41 and 46%, respectively. Interestingly, this incidence was higher than in infants with unilateral CDH [122].

The incidence of CHD in late-presenting CDH patients was reported in five studies and was 9% (53/559) [51,88,95,124,125]. This incidence was significantly lower than that calculated from live-births (p b 0.0001).

Studies based on the Extracorporeal Life Support Organization (ELSO) registry have shown an incidence of CHD in ECMO-treated CDH infants of 1% (17/1318) [30] in 1994, increasing to 9% (316/3342) in 2013 [31]. When considering only "critical CHD", the ELSO registry analysis from 2018 reported an incidence of 3% (197/6696) in CDH infants treated by ECMO [126]. Four other studies reported an incidence of CHD in ECMO treated CDH infants of 5–23% [84,127–129].

Table 4
Cardiac intervention in CDH patients.

	CDH infants who had cardiac intervention	Survival after cardiac surgery
~~Greenwood et al. 1976 [35]~~	~~9% (1/11)~~	~~0% (0/1)~~
Cohen et al. 2002 [23]	23% (6/26)	33% (2/6)
Menon et al. 2013 [17]	8% (59/757)	58% (32/55)
Gray et al. 2013 [21]	30% (12/ 40)	Not specified
Ruano et al. 2015 [19]	28% (6/21)	100% (6/6)
Total	10% (84/855)	59% (40/68)

2.3. Prenatal diagnosis

Eleven studies [52–56,83,96,106,107,115,130] reported the incidence of CHD diagnosed prenatally in CDH fetuses (Table 3). The incidence was found to be 16% (range 4–32%). Another study did not report the total number of CDH fetuses diagnosed prenatally, but described that of the 37 infants with CDH and CHD, 9 had a prenatal diagnosis of CDH and CHD, 9 of CDH alone (CHD detected postnatally), and 6 of CHD alone (CDH diagnosed after birth) [18].

2.4. Management

2.4.1. CDH repair

Overall, 71% of infants with CHD underwent CDH repair, as reported in seven studies [17,19,21,23,35,93,131]. A diaphragmatic repair was carried out in a lower proportion of infants with CHD (72%) compared to those who did not have CHD (85%; p b 0.0001, RR 1.17 [95% CI 1.11, 1.24], I^2 = 4%), as reported in 5 comparative studies (Fig. 2A) [17,19,21,23,93]. The funnel plot of this analysis did not suggest a publication bias, even though the number of studies included was low (Fig. 2B). Three studies reported that a patch repair was required

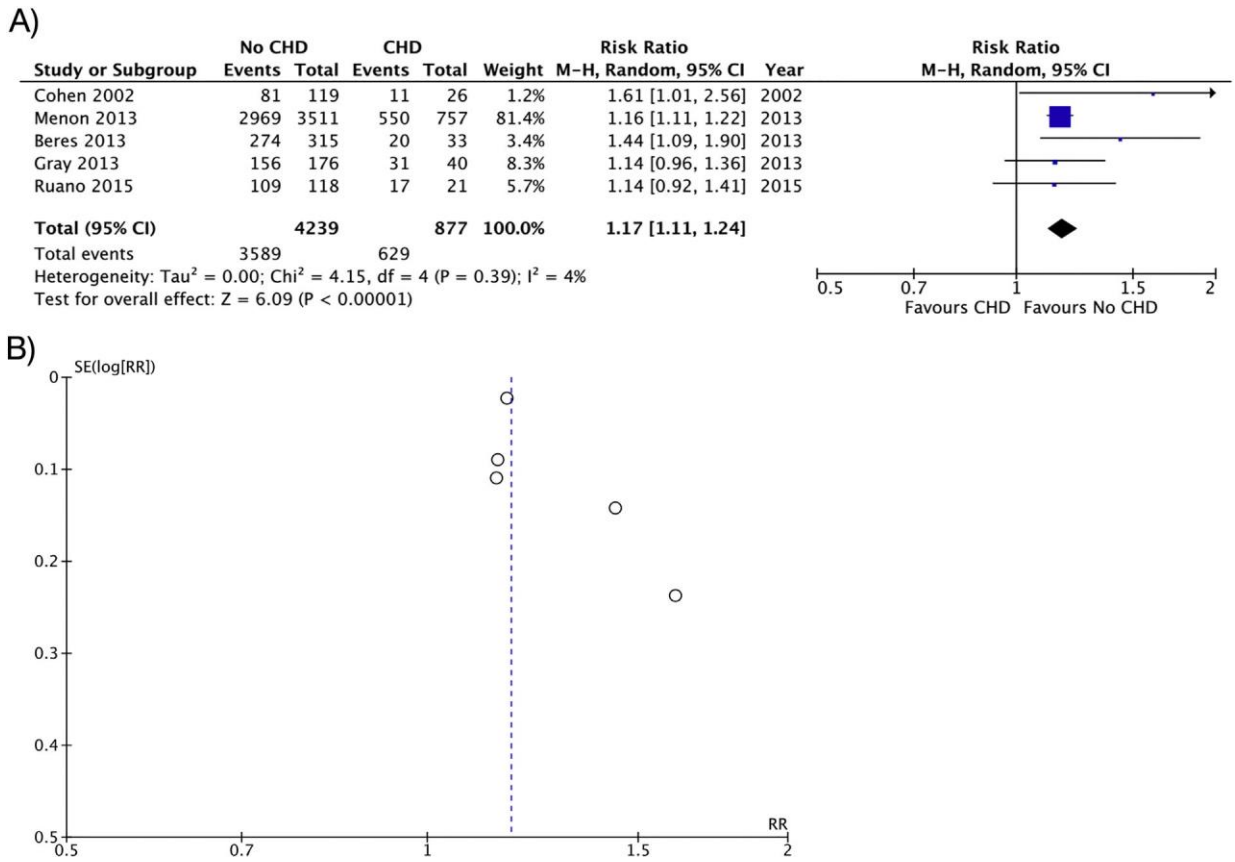

Fig. 2. (A) Forest plot comparison of diaphragmatic repair in CDH infants with and without CHD. (B) Co-respective funnel plot.

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Table 5
Use of ECMO in CDH patients.

	Infants with CHD	Infants without CHD
Menon et al. 2013 [17]	29% (220 /757)	29% (1034/3511)
Gray et al. 2013 [21]	53% (21/40)	39% (69/176)
Takahashi et al. 2013 [20]	7% (5/76)	Not specified
Ruano et al. 2015 [19]	38% (8/21)	34% (40/118)
Total	28% (254/894)	30% (1143/3805)

significantly more often in infants with CHD (39/86, 45%) than in those without (132/434, 30%; p b 0.01) [21,92,132]. Only 5% (9/178) of infants with CHD underwent minimally invasive repair compared to 17% (479/2889; p b 0.0001) of infants without CHD [133].

2.4.2. Cardiac intervention

Five studies (n = 855 CDH patients) reported that 10% (range 8–30%) of infants underwent cardiac intervention (Table 4) [17,19,21,23,35]. Of those who underwent cardiac surgery, 59% (range 0–100%) survived to hospital discharge [17,19,23,35]. CDH repair preceded the cardiac intervention in the majority of cases (83%, 15/18 infants with critical CHD) [21,23].

2.4.3. Use of ECMO

Overall, the use of ECMO in infants with CHD associated to CDH was reported to be 28% in 4 studies (Table 5) [17,19–21]. There was no difference in the use of ECMO, when we considered only the studies that compared infants with isolated CDH (1143/3805 infants, 30%) vs. those with CDH and CHD (249/818 patients, 30%; p = 0.8; Table 5) [17,19,21].

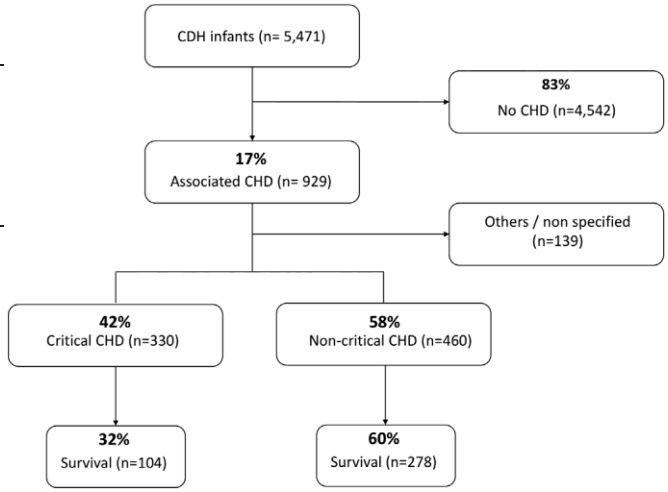

Fig. 3. Survival of infants with CDH associated with CHD.

2.4.4. Use of FETO

Only one study reported the use of FETO in 6 babies with associated CHD (three aortic stenosis, two cases of coarctation of the aorta, and one severe mitral atresia), with a 50% survival to discharge [134].

Table 6
Survival to discharge by type of CHD.

	Survival rate	Infants (n=929)	Survived to discharge (n=469)
Single ventricle	**19%**	**115**	**22**
Hypoplastic left heart syndrome	13%	60	8
Single ventricle (non-specified)	36%	11	4
Double outlet right ventricle (DORV)	22%	32	7
Tricuspid atresia	25%	12	3
Duct-dependent pulmonary circulation	**40%**	**80**	**32**
Tetralogy of Fallot (TOF)	37%	43	16
Pulmonary stenosis (PS) or atresia	52%	21	11
TOF / DORV with PS	31%	16	5
Duct-dependent systemic circulation	**44%**	**87**	**38**
Coarctation of aortic arch	44%	87	38
Total mixing lesions	**20%**	**20**	**4**
Anomalous pulmonary venous return	13%	17	3
Truncus arteriosus	33%	3	1
Non-mixing lesions	**29%**	**28**	**8**
Transposition of great arteries	14%	7	1
Complex two-ventricle (non-specified)	33%	21	7
Shunts	**60%**	**460**	**278**
Ventricular septal defects	59%	222	131
Atrial septal defects	65%	197	129
Atrio-ventricular septal defects	31%	26	8
Patent ductus arteriosus	64%	14	9
Patent foramen ovale	100%	1	1
Others	**40%**	**25**	**10**
Pentalogy of Cantrell	45%	22	10
Absent pericardium	0%	1	0
Heterotaxy syndrome	0%	1	0
Tumor	0%	1	0
Not specified	**68%**	**114**	**77**

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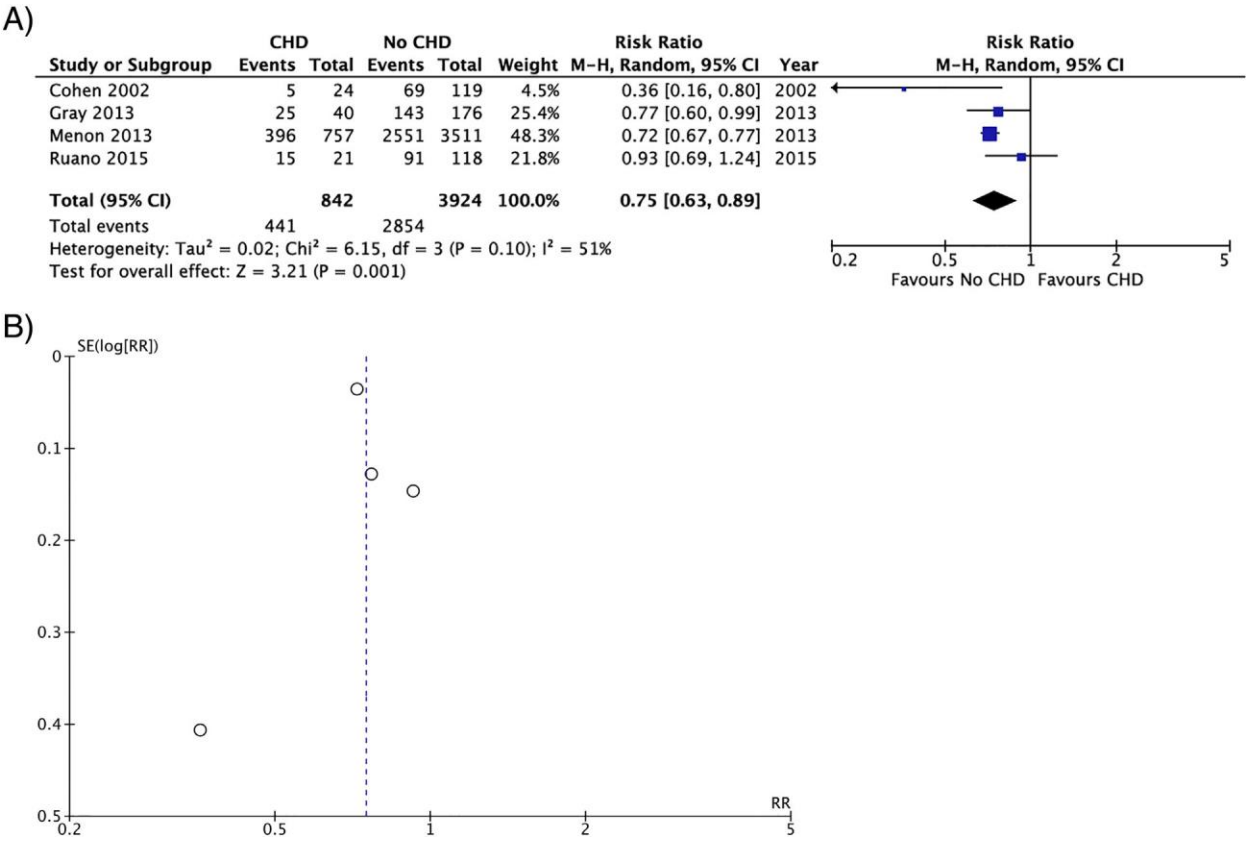

Fig. 4. (A) Forest plot comparison of the survival of CDH infants with and without CHD. (B) Co-respective funnel plot.

2.5. Survival

Six articles met the inclusion criteria [17,19–21,23,35], reporting survival by type of CHD (Table 6). Out of 5471 live births, 929 infants (17%) had a CHD (Fig. 3). When considering only the groups of CHD as predefined in the methods, 42% of the infants with CHD had a critical lesion. Overall, 50% infants with CHD survived to discharge. Out of CDH infants born with critical CHD, 32% survived to discharge. The survival rate was the lowest for CDH patients with a single ventricle and total mixing lesions, and poor for those with duct-dependent circulation and nonmixing lesions. Survival to discharge was higher for noncritical infants with shunts, although it reached only 60%.

In four comparative studies, survival was lower in infants with CHD (52%, 441/842) compared to infants without CHD (73%, 2854/3924, p b 0.001, RR 0.75 [95% CI 0.63–0.89], I^2 = 51%; Fig. 4A) [17,19,21,23]. The funnel plot of these studies demonstrated a convincing symmetry, thus indicating no potential publication bias, even though the number of studies considered was low (Fig. 4B).

2.6. Morbidity

Two studies reported that only 10–13% of infants with CDH and CHD were discharged without any morbidity [3,20].

2.6.1. Cardiac morbidity

The only study reporting long-term cardiac morbidity indicated that none of the CDH patients with CHD seen in the follow up clinic (17/22) had complications or activity restrictions following cardiac surgery [21].

2.6.2. Pulmonary morbidity

At discharge, the incidence of pulmonary morbidity, described as the need for oxygen therapy and/or medications, was higher in infants with CHD (70%; 58/83) than in infants without CHD (602/2100, 29%, p b 0.0001) [3]. The need for pulmonary support at day 30 of life in CDH survivors with an associated CHD was found to be higher (64–82%) compared to infants without CHD (38–46%) [4,135]. Anotherstudy showed that 23% of CDH infants with CHD required oxygen ther-apy at 1 year of life [21].

2.6.3. Neurological morbidity

We found no difference in terms of neurological morbidity at discharge between CDH infants with CHD (25%, 21/83) and those without CHD (20%, 425/2100, p = 0.2) [3].

3. Discussion

The present systematic review of the literature has shown that CHD in babies with CDH is a relevant problem, with a specific impact on the management and outcome of this fragile population of patients. We found a relatively large number of studies either dedicated to or reporting on this relatively rare cohort of infants, although none of them were prospective. To the best of our knowledge, the present study is the first systematic review of the literature on the association between CHD and CDH.

Our review reports that 17% of CDH infants are born with an associated CHD. This incidence equally derives from single institution studies and international multicenter databases. However, we have noticed a strong variation among the selected studies, with an incidence ranging from 3% to 54%. Not surprisingly, when we analyzed studies reporting still-births or pregnancy termination, we found a higher incidence of CHD (27–28%). Moreover, the variation in incidence can be attributed to the definition of CHD. A congenital heart disease has been defined by Mitchell et al. as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or poten- tially of functional significance [136]. However, this definition em- braces a broad spectrum of anomalies, resulting in a population

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differently included in various studies [137]. Furthermore, these studies used different classifications of CHD, either based on the severity of the lesion and hemodynamic significance [17,18,126], based on the requirement for surgical treatment [20], or based on surgical risk, such as RACHS-1 and STS-EACTS scores [7,19,21]. In the present study, we divided the different types of CHD according to their physiology. This is indeed a more pragmatic way, which is commonly used by cardiologists and cardiac surgeons.

Interestingly, we found a similar incidence of CHD in CDH fetuses that were prenatally diagnosed. The majority of the studies selected detected CHD in patients who also had an antenatal diagnosis of CDH. This may be owing to the fact that the diagnosis of CDH is often made at the anatomy scan and is then followed by a fetal echocardiography or magnetic resonance imaging, as scheduled in most protocols.

In this study, we have shown that the presence of a CHD negatively impacts the eligibility for diaphragmatic repair and the modalities of surgery. In fact, the proportion of infants with CDH that underwent surgery was lower if a CHD was associated. This could be owing to the relative instability of their underlying cardiac and pulmonary condition. Not surprisingly, babies with CHD are not good candidates for minimally invasive surgery and often present with large diaphragmatic defect that requires a patch closure. These data come from large comparative studies and represent an important knowledge especially for parental counseling.

In this systematic review, we found that only 10% of infants with associated CDH and CHD underwent cardiac intervention. Although this rate seems low, the proportion of infants with a CHD requiring cardiac surgery was not indicated. Most likely the majority of infants born with an associated CHD suffered from a noncritical lesion that did not warrant neonatal cardiac intervention. Over the last decades, we have witnessed a substantial improvement in the outcome of cardiac surgical neonates with a survival rate for non-CDH neonates undergoing cardiac surgery quoted as N 90% [138]. Conversely, we noticed that of the CDH infants who underwent cardiac surgery, less than 2/3 survived to hospital dis- charge. This confirms that this surgical population is more fragile, possibly suffering from a combination of critical cardiac lesions, pulmonary hypoplasia and pulmonary hypertension. Unfortunately, most selected studies did not report the cause of death, nor the timing and type of cardiac surgery. At present, there are no guidelines to manage babies born with CDH in CHD, but given the rarity of the association and the variable severity of the lesions, it is hard to think that these could be developed.

Neonates with CDH and CHD are treated with ECMO in less than a third of cases, which is comparable with other CDH infants. The use of ECMO in CHD infants undergoing CDH repair has been reported as predictive of lower hospital survival [17]. However, it is difficult to draw conclusions given the intercenter variability in the use of ECMO. FETO is currently the only available prenatal treatment for severe CDH that may improve survival [139]. However, cardiac anomalies which might affect postnatal outcome are currently an exclusion criterion for the ongoing randomized clinical trials on FETO [140]. Interestingly, there have been a few cases of FETO performed in infants with CHD associated with survival [134,141].

The present study has confirmed that the mortality rate of infants with CDH and CHD is higher than that of infants without CHD. Only one third of the infants born with critical lesions survive to discharge. This correlates with the results of a study, where the presence of a major cardiac anomaly (defined in the study according to the RACHS- 1 score) has been reported as being the only independent predictor ofmortality in CDH infants [7]. Moreover, we noticed that although shunts rarely require intervention in the neonatal period, the survival rate of infants with shunts was still lower than the reported survival rate for CDH infants without CHD. Hypoplastic left heart syndrome (HLHS) is the most common single ventricle CHD in patients with CDH, and it has a very low survival rate in this population (13%). Conversely, in in-fants without CDH, the five-year survival rate for HLHS is up to 70% [142]. Balduf et al. suggested that HLHS in mild pulmonary hypoplasiacases should be managed with a Norwood stage I palliation before CDH repair, and that outcome of neonates with CDH and HLHS is deter-mined primarily by the degree of associated pulmonary hypoplasia [143]. The infant will later undergo two other staged surgeries, culmi-nating in a Fontan repair [144]. One study reviewed retrospectively ne-onates with associated CHD and CDH, showing that although 21% of these infants had been eligible for a Fontan procedure, only 5% had pal- liative surgeries and none underwent the Fontan repair [131]. Infants with duct-dependent lesions require immediate treatment in order to maintain pulmonary or systemic circulation and our review shows a survival rate for infants with duct-dependent lesions in association with CDH of 40–44%. The most frequent duct-dependent lesion in CDH patients is a coarctation of the aortic arch, as it represented 9% ofall CHDs. This includes a spectrum of lesions, from interrupted aortic arch to discrete coarctation. Overall postoperative mortality in a recentlarge cohort of infants undergoing coarctation or hypoplastic aortic arch

Table 7
Risk of bias assessment for individual studies using methodological index for nonrandomized studies (MINORS) [27].

Item	Putnam [3]	van den Hout [4]	Menon [17]	Ruano [19]	Takahashi [20]	Gray [21]	Cohen [23]	Green-wood [35]	Beres [93]	Shiono [131]	Brindle [132]	Putnam [133]	Jani [134]	Cauley [135]
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	1	1	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	0	0	0	1	0	2	2	0	0	0	0	0	1	2
7. Loss to follow-up less than 5%	0	0	0	0	0	1	0	0	0	0	0	0	0	1
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	0	2	2	2	1	2	2	1	1	1
10. Contemporary groups	2	2	2	2	2	2	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	1	2	2	0	2	2	2	1	2	1	1	2	2
12. Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	14	13	14	15	10	17	16	14	12	13	12	12	14	16

0 = not reported.
1 = reported but inadequate.
2 = reported and adequate.

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Table 8
GRADE evidence profile [28] for CHD in CDH versus isolated CDH.

Quality assessment							No. of patients		Effect		Quality
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other Considerations	CHD+CDH	Isolated CDH	Relative (95% CI)	Absolute (95% CI)	
CDH repair											
7	OS	Moderate[a]	Low	Not serious	Serious[b]	None	629/877 (71%)	3589/4239 (85%)	RR 1.17 (1.11, 1.24)	140 fewer per 1000 (from 264 fewer to 111 fewer)	⊗⊗OO LOW
CDH repair with patch											
3	OS	Moderate[a]	---	Not serious	Serious[b]	None	39/86 (45%)	132/434 (30%)	---	MD 15.33 higher (from 10.91 higher to 21.29 higher)	⊗⊗OO LOW
ECMO											
3	OS	Moderate[a]	---	Not serious	Serious[b]	None	249/818 (30%)	1143/3805 (30%)	---	MD 5.70 higher (from 0.39 lower to 13.29 higher)	⊗⊗OO LOW
Survival											
4	OS	Moderate[a]	Moderate	Not serious	Serious[b]	None	441/842 (52%)	2854/3924 (73%)	RR 0.75 (0.63, 0.89)	210 fewer per 1000 (from 371 fewer to 57 fewer)	⊗⊗OO LOW
Pulmonary morbidity											
3	OS	Moderate[a]	---	Not serious	Serious[b]	None	199/297 (67%)	1183/3597 (33%)	---	MD 34.84 higher (from 26.61 higher to 41.21 higher)	⊗⊗OO LOW
Neurological morbidity											
1	OS	Moderate[a]	---	Not serious	Serious[b]	None	21/83 (25%)	425/2100 (20%)	---	MD 5.00 higher	⊗⊗OO LOW

OS: observational study; CI: confidence interval; RR: risk relative; MD: mean difference.
GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect;
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
Very low quality: We are very uncertain about the estimate.
[a] Bias owing to possible confounding.
[b] Optimal information size (OIS) not met.

repair was around 2% [73,78]. Conversely, our review has detected an overall survival for these infants of 44%.

Overall, it seems these are infants who would have better survival rates if they were born without CDH. In fact, a recent review on 1000 consecutive neonates who underwent cardiac surgery has reported a survival rate above 90% for the same critical lesions. Although this review was not designed to compare outcomes of infants with associated CHD and CDH with infants with only CHD, it seems undeniable that the presence of CDH, and possibly associated pulmonary hypoplasia and hypertension, is a burden for these patients. Survivors with associated CDH and CHD seem to have increased pulmonary morbidity compared to infants with CDH alone, with an increased rate of infants requiring oxygen for a longer period of time. In these infants, persistent pulmonary hypertension can be secondary to both conditions. Pulmonary hypoplasia of various degrees is known to be associated in infants with CDH. Moreover, a recent study has shown that in fetuses withoutCDH, the presence of CHD with right ventricular outflow tract obstruc-tion was associated with pulmonary hypoplasia [145]. This suggests that some CHD can prenatally participate in the development of pulmo-nary hypoplasia and explain the particularly high mortality in infants with CDH and CHD.

3.1. Limitations

We acknowledge the limitations of this systematic review of the literature whose quality is dependent on the quality of the papers published. Of the articles selected, only a few were designed to specifically address the population of CDH babies with CHD. None of the studies reached the gold standard cut-off on MINORS of 19.8 out of 24 (Table 7). All papers used retrospective data. Nonetheless, some included large number of patients with this rare association, as they were part of multicenter and/or nationwide registries. The studies that were not focused on this population of patients mainly reported the incidence and the outcome of CHD in CDH, whereas more detailed information regarding the surgical management of these infants was not described. Furthermore, a GRADE Evidence Profile table was provided (Table 8). According to GRADE methodol- ogy, the quality of evidence was low for the rate of CDH repair, the requirement of patch repair, the need of ECMO, the percentage of survival, and the incidence of pulmonary and neurological morbidity.

4. Conclusion

In conclusion, the present study shows that CHDs, especially critical lesions, have a strong impact on the management and outcomeof infants with CDH. In fact, the severity of CHD can be considered as an important predictive factor for the morbidity and the mortality of babies with CDH. The combination of CDH and CHD results in much lower survival than in CDH patients without CHD as well as in patients born with isolated cardiac defects. Various aspects of the management of these patients remain controversial. Moreover, no guidelines currently exist for the management of these fragile babies. We believe that there is a need for prospective multicenter dedicated studies that are designed to address some specific aspects of these patients' management.

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