Mortality factors in infants with congenital diaphragmatic hernia: a systematic review

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Abstract (250 words)

BACKGROUND: Congenital diaphragmatic hernia (CDH) is a malformation of the diaphragm accounting for 8% of all major congenital anomalies. While many clinical factors of survival in children with CDH have been established, limited research exists on the role of sociodemographic and other factors. We aimed to systematically identify and summarise all available international literature, published from January 2000 to July 2017, evaluating specific mortality factors for children with prenatally-diagnosed, isolated, left-sided CDH.

METHODS: MEDLINE, PROSPERO, EMBASE, Scopus, The Cochrane Library databases and the table of contents for the past five years for relevant journals were searched systematically. The risk factors of interest were: birth weight, gestational age (GA) at diagnosis, GA at birth, infant sex, maternal age, ethnicity, socioeconomic status (SES) and plurality. The primary outcome measure was survival. Data were extracted on study design, study quality, participant data and survival-related effect estimates.

RESULTS: Seven studies fulfilled the inclusion criteria. In total, 347 children were included in the review. Birth weight, GA at diagnosis and GA at birth were evaluated in five studies each, infant sex in two and maternal age in one. None of these factors were significantly associated with survival. No studies evaluated the influence of plurality, ethnicity or SES.

CONCLUSION: Whilst the factors of interest showed no significant association with survival, more evidence is required to confirm these findings. Understanding whether sociodemographic factors are associated with survival may help inform the development of public health interventions to improve survival rates for children with CDH.

Keywords: congenital diaphragmatic hernia, mortality factors, sociodemographic, public health

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a rare malformation of the diaphragm with an estimated prevalence rate of around 3.5 per 10,000 live births for all CDH cases in the US and 2.3 per 10,000 live births in Europe (McGivern et al., 2015; Shanmugam, Brunelli, Botto, Krikov, Feldkamp, 2017). Around 85-90% of CDH cases correspond to a Bochdalek hernia (Greer, 2013) where there is a large defect within the Bochdalek space of the posterior diaphragm allowing the abdominal contents to herniate into the chest cavity and impairing lung development which results in pulmonary hypoplasia, and consequently morbidity and mortality (Sandstrom & Stern, 2011). A much rarer CDH subtype is Morgagni, comprising 1-5% of the CDH caseload (Simson & Eckstein, 1985). Differences regarding infant and maternal characteristics between CDH subtypes have been noted including: infant sex, mean maternal age, plurality, geographical distribution and survival (Slavotinek & Warmerdam, 2007). Left-sided Bochdalek CDH (LCDH) comprises approximately 85% of cases (Dekoninck et al., 2015), although right-sided CDH (RCDH) has been found to have a greater mortality rate (Skari, Bjornland, Haugen, Egeland, Emblem, 2000), possibly associated with the fact that RCDH is associated with larger defects which also results in greater mortality (Burgos et al., 2017). Additional anomalies are present in around 40% to 60% of all CDH cases (Kaiser & Rosenfeld, 1999), the most common of these being cardiac anomalies which occur in approximately 10% of cases (Fauza & Wilson, 1994).

Advancements in management of CDH (Doyle and Lally, 2004), extracorporeal membrane oxygenation (ECMO) and having the defect surgically repaired are among the clinical factors known to improve survival (Davis et al., 2012). There is further evidence that antenatal parameters such as observed-to-expected (O/E) lung-to-head ratio (LHR), the position of the liver and stomach and the O/E total fetal lung volume are also useful indicators of survival (Mayer et al. 2011; Oluyomi-Obi et al. 2017; Morini, Goldman & Pierro, 2006; Terui et al., 2015). However, these

advances have only led to modest improvements in survival with survival rates remaining around 70% for the past two decades (McGivern et al., 2015; Mah et al., 2009). These clinical factors have been extensively researched and have been the focus of a number of systematic reviews and meta-analyses (Mayer et al. 2011; Oluyomi-Obi et al. 2017; Morini, Goldman & Pierro, 2006; Terui et al., 2015), with sociodemographic factors (e.g. infant sex and socioeconomic status (SES)) only occasionally forming an additional component of the study.

Some literature suggests being from an ethnic minority group (Davis et al., 2012; Aly, Bianco-Batlles, Mohamed & Hammad, 2010), having lower birth weight (Aly et al., 2010), being male (Rocha et al., 2008), and having a lower SES (Davis et al., 2012) impacts on survival, while other studies have reported no association (Aly et al., 2010). However, a key limitation of the current evidence is that the majority of these findings relate to the CDH population as a whole, not accounting for the different classifications of the defect.

Only one existing systematic review with a focus on antenatally-diagnosed infants with isolated CDH, considers the influence on survival from other potential factors (Mayer et al., 2011). Their findings suggested that birth weight was associated with survival but GA at diagnosis or GA at birth were not. However, studies were only included in the review if lung volume or liver position were assessed by fetal MRI (Mayer et al., 2011).

The aim of this review was to systematically identify, appraise and summarise the available contemporary international literature, published from 2000 onwards, relating to selected factors (birth weight, GA at diagnosis, GA at birth, infant sex, maternal age, ethnicity, plurality and SES) that may predict survival for children antenatally diagnosed with isolated, left-sided CDH.

METHODS

A search strategy for database-specific search terms (Appendix I) was developed with an information scientist for the MEDLINE database, and translated across four additional databases:

PROSPERO, EMBASE, Scopus and The Cochrane Library. All related systematic reviews identified were hand searched as were the content lists of the past five years of the most relevant journals in the field of CDH ('Lung', 'Thorax' and 'Journal of Paediatric Surgery').

Inclusion criteria were: peer reviewed full papers published since 2000 (to ensure that the findings were retrieved in accordance with, and relevant to, current care protocols for infants with CDH) in the English language, which examined cohorts of antenatally diagnosed infants with isolated, left-sided CDH and reported on the following factors: birth weight, GA at diagnosis, GA at birth, infant sex, plurality, maternal age, ethnicity, and SES. The studies were required to have a specific outcome related to survival within their specific CDH cohort.

The studies were further limited to only those which had an overall sample size greater than, or equal to 30, as smaller studies are generally considered less robust and are more likely to have lower methodological quality (Sterne, Gavaghan & Egger, 2000).

The searches were carried out between 1st February 2017 and 15th July 2017. Screening titles, abstracts and full papers for inclusion in the review, as well as data extraction and quality assessment using a standardised protocol for data extraction and the Newcastle-Ottawa scale (NOS) (Wells et al., 2013) were carried out by two researchers independently. Independent extractions and assessments were combined and agreed. A third researcher was available for any disagreements (not required). When more than one study analysed data from an overlapping cohort and reported on the same factors, only the most recent study was included. If the studies reported on different risk factors, both studies were included.

The data from the included studies and study quality were summarised and synthesised narratively. When frequency data were available, odds ratios (ORs) for survival and their 95% confidence intervals were calculated using the EpiInfo statistical software. The systematic review was registered on the PROSPERO database (reference CRD42017060888).

RESULTS

The PRISMA flow diagram (Figure 1) demonstrates the systematic review process. Nine retrospective studies were eligible but two multicentre studies were removed due to overlap of data on the same factors.

Figure 1 here

Table 1 presents a summary of the seven included studies (Lazar et al., 2012; Yang et al., 2007; Takahashi et al., 2011; Hidaka et al., 2014; Yamoto et al., 2015; Sananes et al., 2016; Stranak et al., 2017). Data from the same cohort were included in two of these studies (Lazar et al., 2012; Sananes et al., 2016) and the most recent study was used for the factors reported in both studies.

Table 1 here

In six studies, data were collected from one area-specific hospital and one was classified as a national study as all antenatally-diagnosed CDH cases within the country of interest were referred to one specific fetal medicine centre (Stranak et al., 2017). Nine years was the median study length and a total of 347 participants were included in the review.

Limited detail was available relating to the methods applied for ascertainment of data on the risk factors of interest. Only one study detailed that GA was attained using sonographic methods or date of last menstrual period (Yang et al., 2007). Four of the seven studies specified the inclusion and exclusion criteria for the cohort of interest (Yang et al., 2007; Hidaka et al., 2014; Yamoto et al., 2015; Sananes et al., 2016).

The NOS quality scores for the included studies ranged from five to seven (out of a possible 9). The lowest score was associated with including insufficient reporting of length of follow-up and failing to mention how data regarding the factors of interest were ascertained.

Accounting for the overlap between two studies, this review reports on five studies with data for GA at birth (Yang et al., 2007; Takahashi et al., 2011; Hidaka et al., 2014; Sananes et al., 2016; Stranak et al., 2017), five for GA at diagnosis (Yang et al., 2007; Hidaka et al., 2014; Yamoto et al.,

2015; Sananes et al., 2016; Stranak et al., 2017), two for infant sex (Hidaka et al., 2014; Yamoto et al., 2015) and one for maternal age (Sananes et al., 2016). Table 2 shows the risk factor data available for each of the included studies. No data were provided in any of the included studies related to plurality, year, parity, maternal ethnicity or SES.

Table 2 here

All studies reported the overall survival rate for infants with CDH which ranged from 59% (Yang et al., 2007) to 84.4% (Hidaka et al., 2014), although they are not easily comparable due to the difference in the chosen follow-up period. Two studies did not report how long the survival outcome was measured for (Takahashi et al., 2011; Yamoto et al., 2015), three reported survival until hospital discharge (Yang et al., 2007; Hidaka et al., 2014; Stranak et al., 2017). Of these, none defined how long the average hospital inpatient time was prior to discharge. The remaining two studies with overlapping data monitored infants for six months (Lazar et al., 2012; Sananes et al., 2016).

Five studies evaluated the association of birth weight and survival (Lazar et al., 2012; Takahashi et al., 2011; Hidaka et al., 2014; Yamoto et al., 2015; Stranak et al., 2017). Four studies measured birth weight continuously (Table 3) and three of these studies found that the mean or median birth weight was lower within the non-survivor group when compared to the survivor group, although only one reported a statistically significant difference (p<0.01) (Yamoto et al., 2015). One study (Takahashi et al., 2011) measured birth weight categorically (≤2,500g or >2,500g) and reported a statistically significant difference in survival between the two subgroups (p < 0.01), with 75% survival among the infants with higher birth weight compared with 60% survival in the lower birth weight group.

Table 3 here

Five studies presented data regarding GA at diagnosis for survivors and non-survivors.[Yang et al., 2007; Hidaka et al., 2014; Yamoto et al., 2015; Sananes et al., 2016; Stranak et al., 2017). Only one

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study (Yamoto et al., 2015) reported a statistically significant association between continuous GA at diagnosis and survival (p=0.02). In one study (Yang et al., 2007), GA at diagnosis was categorised in <25 weeks (69%), and ≥25 weeks (53%) but the difference did not reach statistical significance (OR 1.26, 95% CI 0.54-2.94).

Five studies reported the effect of GA at birth on survival (Table 3) where the differences between surviving and non-surviving were all non-significant (p>0.05). In addition to reporting GA at birth continuously, Yang et al. (2007) divided their cohort into those born prematurely (24%), classified as before 34 weeks, and those born at or after 34 weeks. While 50% of the non-premature children survived, 63% of the premature children died but this difference was not statistically significant (OR 1.70, 95% CI 0.70-4.15).

Table 4 shows the results from two studies which investigated the association between survival and infant sex (Hidaka et al., 2014; Yamoto et al., 2015). In both studies, the difference in survival related to infant sex was not statistically significant.

Table 4 here

Sananes et al. (2016) reported a non-statistically significant difference (p=0.903) in maternal age for survivors (mean: 27.7 years, sd: 6.0) and non-survivors (mean: 27.9, sd: 7.4).

DISCUSSION

This study examined the contribution of selected factors on mortality in infants with antenatally-diagnosed, isolated, left-sided CDH. In the small number of included studies, birth weight, GA at diagnosis and at birth, infant sex and maternal age did not have a statistically significant impact on survival. In addition, no studies examined the influence of other important non-clinical factors such as plurality, parity, maternal ethnicity or SES on survival.

Although thirty studies were identified, only nine reported on the specific factors of interest, with two of these fully excluded due to overlapping data. It was expected that these studies would focus

on antenatal diagnostic factors for survival. However, it was not anticipated that studies would not include data for routinely collected data such as infant sex and maternal age.

It has been widely established that a lower birth weight substantially increases an infant's risk of mortality (McCormick, 1985). Whilst, on average, birth weight was slightly lower in non-survivors, the finding was only statistically significant in one of the five studies that examined its influence (Yamoto et al., 2015). This non-significance contrasts with other antenatal studies which have addressed birth weight as a potential risk factor for survival (Frenckner, Lally , Hintz , Lally & Congenital Diaphragmatic Hernia Study Group, 2007) and also differs from the systematic review by Mayer et al. (2011). Overall, birth weight in the identified studies had a mean or median value of 2500g or greater and even the average birth weight within the non-survivor group was also greater than this cut-off in two studies (Lazar et al. 2012; Hidaka et al. 2014). Improvements in antenatal care, owing to a greater proportion of infants born at normal birth weight, might be an explanation.

It has been suggested that the higher mortality within antenatally diagnosed infants is the result of the more severe cases of CDH being detected by antenatal scans (Adzick et al. 1989), which could indicate an association between worse survival and an earlier GA at diagnosis. However, only one study found an association between GA at diagnosis and survival in this review. This lack of an association was also observed in a large Australian population-based study (Colvin, Bower, Dickinson & Sokol, 2005). Possibly, the fact that the majority of cases of CDH are mainly diagnosed within a specific time interval of the antenatal period (Garne et al., 2002), reduces the effect of this factor, in addition to an earlier diagnosis giving more time and opportunity for antenatal and postnatal care planning.

GA at birth was marginally lower in non-survivors but the difference was not found to be statistically significant. These findings are similar to a Croatian population-based study of all infants with CDH (Grizelj, et al., 2016) which investigated this factor in antenatally diagnosed infants with an isolated defect. This might result from the fact that when studies exclude those who

have received a fetal intervention (Sananes et al., 2016) and those with termination of pregnancy or associated anomalies, which was an eligibility criteria, the likelihood of birth occurring at the correct GA is higher (Mayer et al., 2011). This might also explain the non-significant findings related to birth weight, a factor which is strongly related to GA at birth (Callaghan & Dietz, 2010). Infant sex also did not show an association with survival, which agrees with other studies in infants with CDH (Aly et al., 2010; Berlit et al., 2012).

The relationship with survival is likely to be a complex, synergistic combination of various factors which culminate in either infant death or survival, and if survival, an incurred level of morbidity. As mortality rates persist in children born with CDH, some factors, or combinations of factors contributing to survival, have not yet been identified. As such, research regarding survival should attempt to assess sociodemographic and other characteristics alongside clinical factors. This review illustrates the disparity of this approach within studies of this infant subgroup. Further evidence that this is necessary can be seen when looking at other congenital anomalies, such as congenital heart disease, where it is observed that prognosis is often related to the factors studied within this review (Best, Tennant & Rankin, 2017).

As a result of the limited number of studies, the non-significance of the results need to be interpreted carefully and an increase in the number of studies and consistency in the presented statistics, to allow meta-analysis, is required for more robust conclusions.

Strengths

The process for literature searching was detailed and extensive. The review searched five databases, as evidence suggests the searching of only a single database will retrieve approximately forty percent of relevant articles (Lawrence, 2008). The search strategy also included searching the table of contents for key journals which were likely to have content relevant to survival within CDH. This is recommended to help identify any articles missed during online database searching (Helmer, Savoie, Green & Kazanjian 2001).

The review focussed on a very specific subset of infants, the most prevalent subgroup within the field of CDH, which ensures that the findings are more robust and less affected by study heterogeneity (O'Connor, Green & Higgins, 2008), although it reduces the generalisability of the findings. The fact that the studies did not assess the factors of interest as their primary objective may have had a beneficial impact by reducing bias as the non-significant findings were still included. Also, studies with a sample size of 30 or greater are often considered as more robust, with improved methodological quality, and increased likelihood of publication regardless of their findings (Sterne, Gavanhan & Egger, 2000).

Limitations

The exclusion of studies in languages other than English might result in not accounting for potentially relevant results. In addition, the differences in the statistical measures which studies used to report the effect on survival also hindered the use of meta-analytic techniques and assessment of publication bias.

CONCLUSION

Whilst maintaining a focus on clinical antenatal diagnostic factors has resulted in subtle improvements, the survival of infants with isolated, left-sided CDH has remained static. Steps should be taken for this information to be collected and reported routinely and further studies are needed to investigate other sociodemographic and non-clinical factors that may impact on survival. Understanding the impact of these factors may help to inform the development of public health interventions to improve survival rates for children with CDH.

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Table 1 – Summary of the main characteristics of the included studies

Study	Geographical Location	Study Period	Number of infants with CDH	NOS Quality Score§
Yang et al. (2007)	University of California, San Francisco, USA	March 1995 – June 2004	107	6
Takahashi et al. (2011)	Jutendo University School of Medicine, Tokyo, Japan	2002 – 2009	39	6
Lazar et al. (2012)	Texas Children's Hospital Houston, USA	January 2004 – December 2010	53	7
Hidaka et al. (2014)	Osaka Medical Center and Research Institute for Maternal and Child Health, Izumu, Japan	2006 – 2011	32 †	5
Yamoto et al. (2015)	Shizuoka Children's Hospital, Japan	January 1997 – July 2014	33‡	6
Sananes et al. (2016)	Texas Children's Hospital Houston, USA	January 2004 – April 2014	77	7
Stranak et al. (2017)	Fetal Medicine Centre, Prague, Czech Republic (all antenatally diagnosed cases referred here)	June 2003 – May 2015	59	6

CDH: Congenital diaphragmatic hernia

NOS: Newcastle- Ottawa scale

† Additionally, another 34 control subjects with normal thorax

‡ Additionally, another 99 control subjects who were healthy infants

§ Calculated as an average of the total quality scores for each factor of interest included in the study. Scored out of 9.

Table 2 – Summary of risk factors and survival in overall cohort for the included studies

Study	N	Birth weight[†] (g)	GA at diagnosis[†] (wks)	GA at birth[†] (wks)	Infant sex - Male	Maternal Age (years)	Survival Rate (%)	Follow-Up Period
Yang et al. (2007)	107			37.7 (25.7-41.4)			59.0	Hospital Discharge
Takahashi et al. (2011)[‡]	39							NR
	≤2500g N =15	2321 ± 152		38.2 ± 1.014	6 (40%)		60.0	
	>2500g N=24	2986 ± 412		37.5 ± 1.021	17 (71%)		75.0	
Lazar et al. (2012)	53[§]	NR	23.0 ± 5.6[§]	[§]		27.7 ± 6.1[§]	[§]	6 months
Hidaka et al. (2014)	32	2623 (1834-3324)	28 (19-36)	37 (33-40)	17 (53%)		84.4	Hospital Discharge
Yamoto et al. (2015)	33	NR	NR		21 (64%)		60.6	NR
Sananes et al. (2016)	77		NR	37.6 ± 1.6 (32 – 40)		NR	79.3	6 months
Stranak et al. (2017)	59	2816 (990-3,900)	25 (20-38)	38 (27-41)			72.9	Hospital Discharge[c]

NR: not reported

GA: Gestational Age

[†] Data expressed as either: Mean ± Standard Deviation *or* Median and (Range)

[‡] Children without need for respiratory support, tube feeding and parenteral nutritional support

[§] Overlapping data with *Sananes et al., 2016* therefore not included in analysis

Table 3– Summary of findings regarding studies which evaluated continuous birth weight, GA at diagnosis and GA at birth and its relationship with survival outcome

| | Reported Values for Birth weight (g) | | Statistical Comparison between Survivor and Non-Survivor Groups | | | | |
| | | | Odds Ratio | | | Difference in Means/Medians | |
Study	Survivors[†]	Non-Survivors[†]	Value	95% CI	P-Value	Diff. in Means P-Value	Diff. in Medians P-Value
Birth weight (grams) - Continuous							
Lazar et al. (2012)	2957.2 ± 567.2	2858.3 ± 453.4				0.63	
Hidaka et al. (2014)	2622 (1834-3324)	2670 (2372-3308)					NS
Yamoto et al. (2015)	2828 (2368-3390)	2350 (1874-3240)					<0.01
Stranak et al. (2017)	2755 ± 723	2333 ± 919				0.069[§]	
Gestational Age at Diagnosis (weeks) - Continuous							
Hidaka et al. (2014)	28 (19-37)	27 (23-31)					NS
Yamoto et al. (2015)	27.7 (19-37)	24.2 (17-34)					0.02
Sananes et al. (2016)	26.8 ± 5.4	26.7 ± 5.4				0.928	
Stranak et al. (2017)	26.3 ± 5.1	26.4 ± 5.3				0.978[§]	
Gestational Age at Birth (weeks) - Continuous							
Yang et al. (2007)	38.0 (27.3-40.9)	37.1 (27.4-41.4)	1.04[‡]	0.90-1.19	NS		NS
Hidaka et al. (2014)	37 (33-40)	37 (37-38)					NS
Yamoto et al. (2015)	37.4 (36-40)	36.4 (34-38)					0.07
Sananes et al. (2016)	37.6 ± 1.7	37.6 ± 1.0				0.967	
Stranak et al. (2017)	37.2 ± 2.9	35.7 ± 4.5				0.244[§]	

NS: non-significant

SD: standard deviation

CI: Confidence interval

g: grams

[†] Data expressed as either: Mean ± Standard Deviation *or* Median and (Range)

[‡] adjusted for liver herniation, fetal surgery, GA at delivery, GA at LHR measurement and ECMO therapy.

[§] Chi-square test

Table 4 – Summary of findings regarding studies which evaluated infant sex and its relationship with survival outcome

| Study | Participant Groups | Number of Participants | | | Odds Ratio | | Chi-Squared / Fisher's Exact |
		Total No.	No. of Survivors (%)	No. of Non-Survivors (%)	Value	95% CI	P-Value
Hidaka et al. (2014)	Male	17	16 (94)	1 (6)	*5.82*	*0.57-59.32*	0.14
	Female	15	11 (73)	4 (27)			
Yamoto et al. (2015)	Male	21	12 (57)	9 (43)	*0.67*	*0.15-2.93*	0.59
	Female	12	8 (67)	4 (33)			

CI: Confidence interval

Figure 1 – PRISMA flow diagram of the systematic review process

Appendix I – Search Strategies for Each Database

Ovid MEDLINE® 1946 to 2017, July Week 2:
1. (exp hernia/ or hernia*.mp.)
2. ("congenital, hereditary, and neonatal diseases and abnormalities"/ or congenital abnormalities/ or exp digestive system abnormalities/ or exp respiratory system abnormalities/ or exp infant, newborn, diseases/ or malformation.mp. or congenital.mp or exp child/ OR exp minors/ OR exp infant/ OR child*.mp OR infant*.mp OR (baby or babies).mp OR newborn*.mp OR neonat*.mp OR infant.mp OR toddler*.mp.)
3. (Diaphragm/ or diaphragm*.mp.)
4. 1 and 2 and 3
5. (bochdalek or morgagni).mp.
6. (Hernias, Diaphragmatic, Congenital/)
7. 5 or 6
8. 4 or 7
9. Mortality, Premature/ or Fetal Mortality/ or exp Infant Mortality/ or Child Mortality/ or Hospital Mortality.mp. or Death/ or Cause of Death/ or Perinatal Death/ or Fetal Death/ or exp Infant Death/ or exp Fatal Outcome/ or death.mp. or mortal*.mp. or mo.fs. or exp Treatment Outcome/ or outcome*.mp. or exp Prognosis/ or prognos*.mp. or exp Survival Analysis/ or surviv*.mp. or exp prenatal diagnosis/ or exp Fetal Therapies/
10. 8 and 9
11. Limit 10 to humans

EMBASE 1974 to 15th July 2017:
1. (exp hernia/ or hernia*.mp.)
2. (Congenital Disorder/ OR agenesis and aplasia or congenital lung disease/ or fetus diseases/ or exp prenatal disorder/ or fetus malformation/ or congenital.mp or exp child/ OR minor person/ OR exp infant/ OR newborn/ OR child*.mp OR infant*.mp OR (baby or babies).mp OR newborn*.mp OR neonat*.mp OR infant.mp OR toddler*.mp)
3. (Diaphragm/ OR exp diaphragm disease/ or diaphragm*.mp)
4. 1 and 2 and 3
5. (bochdalek.mp OR morgagni.mp)
6. (bochdalek hernia/ or congenital diaphragm hernia/)
7. 5 or 6
8. 4 or 7
9. exp Mortality Rate or mortality/ or childhood mortality/ or embryo mortality/ or fetus mortality/ or hospital mortality/ or infant mortality/ or exp mortality rate/ or exp perinatal mortality/ or premature mortality/ or prenatal mortality/ or standardized mortality ratio/ or surgical mortality/ or death/ or "cause of death"/ or exp child death/ or exp fetus death/ or perinatal death/ or adverse outcome/ or exp treatment outcome/ or death.mp or prognosis/ or exp survival/ or exp survival analysis/ or surviv*.mp. or exp prenatal diagnosis/ or Fetal Therapy/
10. 8 and 9
11. Limit 10 to humans

Scopus 1995 to July 2017:

1. (TITLE-ABS-KEY (*congen** OR *fetal* OR *infant*))
2. (TITLE-ABS-KEY (*diaphragm** OR *bochdalek* OR *morgagni*))
3. (TITLE-ABS-KEY (*hernia**))
4. (TITLE-ABS-KEY (*mortal** OR *death* OR *outcome* OR *prognos** OR *surviv**))
5. 1 and 2 and 3 and 4

The Cochrane Library (1999 to 15th July 2017):

1. MeSH descriptor: [Hernias, Diaphragmatic, Congenital] this term only
2. (congen* or " fetal disease") and (diaphragm* or bochdalek or morgagni) and (hernia*)
3. (mortal* or death or outcome or prognos* or surviv* or treatment)
4. #2 and #3
5. #1 or #4
6. Excl. 'economic evaluations' and 'Cochrane group'