ORIGINAL ARTICLE

Outcomes of patients with exomphalos and associated congenital heart diseases

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Abstract

Introduction Exomphalos is an anterior abdominal wall defect resulting in herniation of contents into the umbilical cord. Severe associated chromosomal anomalies and congenital heart disease (CHD) are known to influence mortality, but it is not clear which cardiac anomalies have the greatest impact on survival.

Methods We performed a retrospective review of the treatment and outcome of patients with exomphalos over a 30-year period (1990–2020), with a focus on those with the combination of exomphalos major and major CHD (EMCHD).

Results There were 123 patients with exomphalos identified, 59 (48%) had exomphalos major (ExoMaj) (defect > 5 cm or containing liver), and 64 (52%) exomphalos minor (ExoMin). In the ExoMaj group; 17% had major CHD (10/59), M:F 28:31, 29% premature (< 37 weeks, 17/59) and 14% had low birth-weight (< 2.5 kg, 8/59). In the ExoMin group; 9% had major CHD (6/64), M:F 42:22, 18% premature and 10% had low birth-weight. The 5-year survival was 20% in the EMCHD group versus 90% in the ExoMaj with minor or no CHD [$p < 0.0001$]. Deaths in the EMCHD had mainly right heart anomalies and all of them required mechanical ventilation (MV) for pulmonary hypoplasia prior to cardiac intervention. In contrast, survivors did not require mechanical ventilation prior to cardiac intervention.

Conclusion EMCHD is associated with high mortality. The most significant finding was high mortality in those with right heart anomalies in combination with pulmonary hypoplasia, especially if pre-intervention mechanical ventilation is required.

Keywords Exomphalos major · Congenital heart disease · Pulmonary hypoplasia · Mechanical ventilation

Introduction

Exomphalos is an anterior abdominal wall defect affecting 1 in 5000 neonates [1]. Exomphalos has traditionally been defined as either exomphalos major (ExoMaj) with a defect larger than 5 cm in diameter and/or including the liver, or exomphalos minor (ExoMin) with a defect smaller than 5 cm. There is a large abdomino-visceral disproportion in ExoMaj, which may make reducing sac contents into the abdomen difficult or impossible [2, 3]. Up to 75% of patients have other congenital anomalies associated with exomphalos, including congenital heart diseases (CHD),

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chromosomal anomalies (esp. trisomy 13 and 18) and Beck-with-Wiedemann syndrome, and, rarely, midline syndromes [4–7].

CHD may be seen in 30–50% of foetuses with exomphalos which include minor lesions such as small ventricular or atrial septal defects (ASDs/VSDs) but can also be complex in nature [8, 9]. Mortality in ExoMaj ranges between 4 and 37% [10–13] with pulmonary hypoplasia as the main contributing factor to morbidity and mortality as well as associated chromosomal disorders, major cardiac defects, and feeding difficulties [4, 10]. Infants with giant exomphalos suffer greater mortality than those with minor defects. Mortality is commonest in those with ExoMaj born at lower gestational age and birth weight [14, 15].

It has been reported that major CHD, defined as those who require intervention in the first year of life, can be the major factor contributing to poor prognosis in neonates with exomphalos, with 2.4 times higher mortality rate in the first year compared to infants with isolated exomphalos [16]. However, it has also been reported that CHD does not appear to affect overall surgical outcomes for exomphalos [3]. In this retrospective 30-year analysis, we aim to describe a single centre experience in exomphalos with a specific focus on the outcomes of patients with ExoMaj and major CHD (EMCHD).

Methods

Neonates with exomphalos admitted to our hospital, over a 30-year period between 30th September 1990 and 30th September 2020, were identified using International Statistical Classification of Diseases, 10th version (ICD-10) for diagnosis of exomphalos, and cardiac database (Heartsuite) for diagnosis of cardiac anomalies, in our tertiary children hospital.

Those who died in-utero or had a termination of pregnancy were excluded. Case notes were further studied to analyse outcomes. The demographic characteristics such as sex, gestational age, birth weight, genetic diagnosis, cardiac diagnosis, and associated non-cardiac condition for patients diagnosed with ExoMaj and ExoMin were analysed. Over the last 10 years, we have standardised dressing with Manuka honey (non-adherent viscose net dressing coated with 99% Manuka honey and 1% Manuka oil) to encourage epithelialisation and then attempt surgical reduction and repair of the abdominal defect at 1 year of age [2].

The patients were divided into two groups: ExoMaj and ExoMin. CHD was found in both groups, and those with exomphalos with CHD were further sub-grouped based on the severity of the CHD (major CHD vs minor CHD). We defined major CHD as those requiring (or likely to require) intervention in the first year of life. Those whom we were not

able to find documented echocardiographic findings of CHD are considered to have either normal heart or a minor CHD as there were no clinical concerns of CHD. Mechanical ventilation (MV) is defined as need for mechanical ventilation for any period of time. Prolonged MV is defined as ≥ 21 consecutive days of ventilation for ≥ 6 h per day [17]. Survival outcome data were obtained and censored at 16 years of age, when they are usually transitioned to adult care, or on 30 June 2021 when data collection for follow-up data were completed.

Data were collected and analysed using Microsoft Excel [Microsoft corporation, Redmond, USA] and R (version 4.0.2) [R Project for Statistical Computing, Austria] [18]. Numerical data were summarised as either mean $\pm$ standard deviation or median $\pm$ interquartile ranges (IQR) as appropriate. Categorical data were summarised as counts and percentages. Chi-square test was used to test for significance between difference in survival outcomes between the groups. Survival curves were drawn using RStudio using Survminer package [19]. The *p* values stated in the Kaplan–Meier Survival plots were derived from log-rank test. A *p* value < 0.05 was considered statistically significant. Association of survival outcomes with exomphalos group and congenital heart disease group were also analysed in a limited multivariable logistic regression analysis.

Results

Patients' distribution and demographics

A total of 123 children with exomphalos were identified (Fig. 1); 59 (48%) were ExoMaj and 64 (52%) were ExoMin. In the ExoMaj group; 10/59 (17%) were found to have major CHD (EMCHD) whereas 25/59 (42%) had minor CHD. Eighteen (31%) had normal cardiac screening. We were not able to identify a cardiac diagnosis in the remaining 6 (10%) patients. Twenty-eight of the 59 (47%) were males, 17/59 patients (29%) were born premature (less than 37 weeks' gestation) and 8/59 patients (14%) had a low birth weight (< 2.5 kg). In the ExoMin group; 9% had major CHD (6/64), 42/64 (65%) were males, 11/64 (18%) were born premature and 7/64 (10%) had low birth-weight.

Genetic and non-cardiac diagnosis

Genetics testing (karyotype and chromosomal microarrays) was done on 29/59 (49%) in the ExoMaj group; 6/10 (60%) in the EMCHD group and 23/49 (47%) in the ExoMaj with minor or no CHD group. Seven of the 23 patients tested in ExoMaj with minor or no CHD had a genetic abnormality, including neurofibromatosis type1, tyrosine-protein phosphatase non-receptor type 11 (PTPN11) mutation,
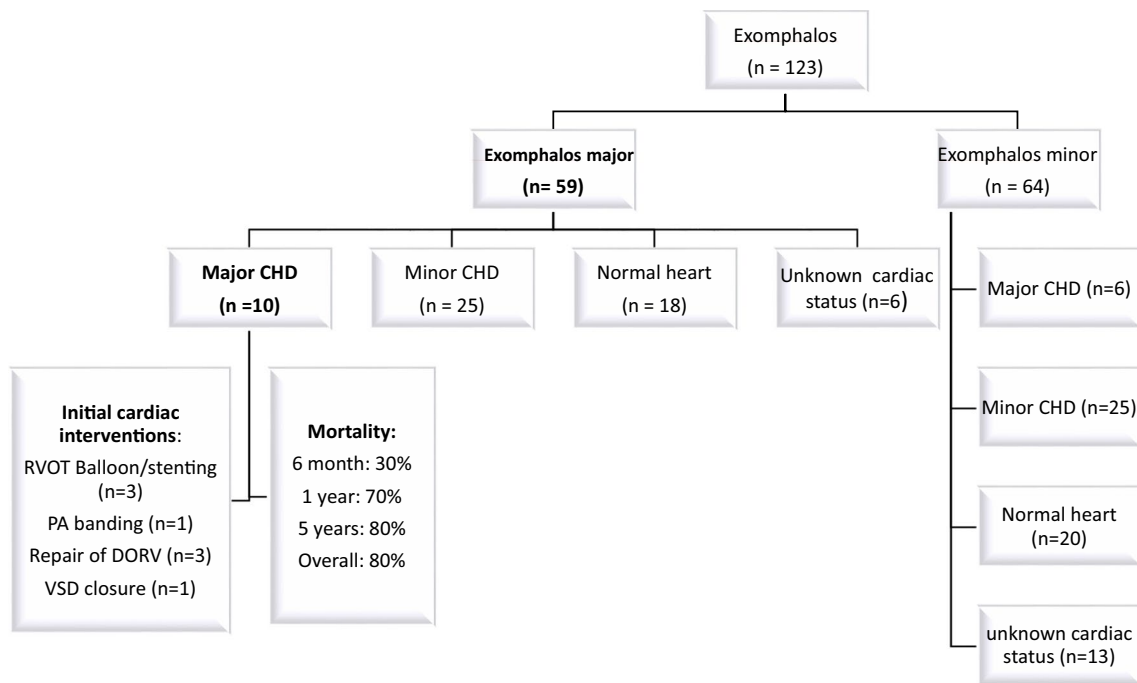
Fig. 1 Description of congenital heart diseases in patients with exomphalos major and minor. *CHD* congenital heart diseases, *DORV* double-outlet right ventricle, *PA* pulmonary artery, *RVOT* right ventricular outflow tract, *VSD* ventricular septal defect

unbalanced translocation of 7p and 9p chromosomes, and Beckwith-Wiedemann syndrome ($n = 4$). None of the 6 patients tested in the EMCHD had genetic abnormalities.

Non-cardiac diagnosis was identified in 28/59 (47%) patients in the ExoMaj group, 8 of them were in the EMCHD sub-group (Table 1); these included pulmonary hypoplasia, chronic lung disease, hypoxic-ischaemic encephalopathy, cleft palate, skeletal abnormalities, vertebral abnormalities, gastro-oesophageal reflux, optic pathway gliomas, inguinal hernia, hydronephrosis, bladder exstrophy, anorectal malformation, and undescended testicles.

Antenatal diagnosis

Foetal diagnosis of exomphalos was possible in 45/59 (76%) patients in the ExoMaj group. Foetal diagnosis of cardiac abnormality was found in 9/59(15%) patients of this group. Five of the 10 patients with EMCHD had antenatal diagnosis of CHD, and 8/10 had antenatal diagnosis of either ExoMaj or major CHD, or both.

Survival rates

The median follow-up duration was 10 years (4–16), until 30th June 2021. In patients with ExoMaj: six month survival for EMCHD group versus ExoMaj with minor or no CHD group was 7/10 (70%) versus 46/49 (94%). One-year survival for EMCHD versus ExoMaj with minor or no CHD was

(3/10) 30% versus (45/49) 92%. And, 5-year survival for the EMCHD versus ExoMaj with minor or no CHD group was 2/10 (20%) versus 44/49 (90%) [$p < 0.0001$].

For the ExoMin group: 5-year survival was 6/6 (100%) for patients with ExoMin with major CHD versus 56/58 (96%) for those with ExoMin with minor or no CHD.

Figure 2 shows the Kaplan–Meier survival plots in the two exomphalos groups.

Given only 15 deaths were observed in the dataset, a limited multivariable regression analysis exploring association of only two main explanatory variables (ExoMaj/ExoMin and CHD major/minor/none) of interest with deaths was performed (Fig. 3). Odds ratios (OR) of survival (95% CI) for CHD minor and CHD none were 4.6 (1.2–19.8), $p = 0.03$ and 39.3 (5.6–811), $p = 0.001$ respectively compared with CHD major as reference group; and ExoMin had an OR of 7.8 (1.8–55.4), $p = 0.01$ compared with ExoMaj as reference group in the multivariable analysis. Figure 3 gives model predictions showing probabilities for 5-year survival with 95% confidence intervals for the two variables of interest.

Presentation time span and "era-effect"

Regarding the time of presentations; 18/59 (31%) ExoMaj patients presented in the first 15 years of the study period, of which 4 had major CHD, and 3 out of those 4 died. The later 15 years had 41/59 (69%) ExoMaj cases, 6 had major CHD, and 5 out of those 6 died. The most recent 5 years

Table 1 Details of mortality cases of exomphalos major and significant CHD

No	Cardiac diagnoses	Other comorbidities	Genetic diagnosis	Need for mechanical ventilation	Surgical (exomphalos) Interventions	Cardiac interventions	Age at death (D, W, M, Y)
1	TOF	Pentalogy of Cantrell	Not done	MV prior to cardiac intervention	Exomphalos repair (D1)	TOF repair (D1)	2D
2	Large inlet VSD and PDA		Normal genetics	MV not needed	Exomphalos repair (D1)	VSD closure and PDA ligation (5W)	Alive
3	TOF	Prematurity Chronic lung diseases Pentalogy of Cantrell Gastroesophageal reflux	Normal genetics	PMV prior to cardiac intervention	Exomphalos repair (1W)	Balloon dilatation of RVOT and RPA (2M), Repair of TOF (6M)	9M
4	Multiple VSDs	Chronic lung disease Pulmonary hypoplasia	Not done	PMV prior to cardiac intervention	Exomphalos repair (D1)	Pulmonary artery banding (6W)	9M
5	DORV, Fallot's type Bilateral superior venae cavae	Pentalogy of Cantrell, Tracheobronchomalacia Chonala atresia (operated)	Normal genetics	PMV prior to cardiac intervention	CM until combined cardiac and exomphalos surgery	Combined cardiac and exomphalos surgery (2Y9M)	2Y, 9M
6	Supracardiac TAPVC	Right hydronephrosis, Absent left thumb	Not done	MV needed, extubated at home	CM		13D
7	DORV, Fallot's type	Pentalogy of Cantrell Chronic lung disease Intrauterine growth restriction Seizures	Not done	PMV prior to cardiac intervention	CM	RVOT stent (2M), Balloon dilatation of RVOT stent and LPA (6M)	7M
8	DORV, Fallot's type	Pentalogy of Cantrell Seizure	Normal genetics	MV not needed	Exomphalos repair (3Y)	Repair of DORV (4W)	Alive
9	DORV, Fallot's type		Normal genetics	PMV prior to cardiac intervention	CM	No intervention	17D
10	TOF	Pulmonary hypoplasia, Tracheostomy	Normal genetics	PMV prior to cardiac intervention Y	First stage multilayer closure of exomphalos (7M)	RVOT stent attempted (2M)	11M

CM conservative management, *D* days, *DORV* double-outlet right ventricle, *ECMO* extra-corporeal membranous oxygenation, *LPA* left pulmonary artery, *LSVC* left superior vena cava, *M* months, *MV* mechanical ventilation, *PMV* prolonged mechanical ventilation, *PS* pulmonary stenosis, *RPA* right pulmonary artery, *RVOT* right ventricular outflow tract, *TAPVD* total anomalous pulmonary venous drainage, *TOF* Tetralogy of Fallot's, *VSD* ventricular septal defect, *W* weeks, *Y* years

produced 16/59 (27%) ExoMaj cases, 2 had major CHD, and both died.

Outcomes of EMCHD

Ten patients were found to have EMCHD (Table 1). The cardiac anatomy was as follows; 4 had double-outlet right ventricle (DORV Fallot type), 3 had tetralogy of Fallot's (TOF), 2 with haemodynamically significant ventricular septal defects (VSD), and 1 with total anomalous pulmonary venous connection (TAPVC).

For exomphalos management; 5 patients were treated conservatively, and the remaining 5 had primary repair of ExoMaj (3 repaired on day 1, 1 repaired on day 7, and 1 repaired at 2 months).

For initial cardiac interventions; 1 patient had VSD closure, 1 had pulmonary artery (PA) Band, 3 had primary repair of DORV/ TOF, and 3 catheters interventions (including 1 RVOT stent, 1 attempted stent (failed), and 1

Fig. 2 Kaplan-Meier survival curves for exomphalos major with and without major CHD (A) and exomphalos minor with and without CHD (B); CHD; congenital heart disease
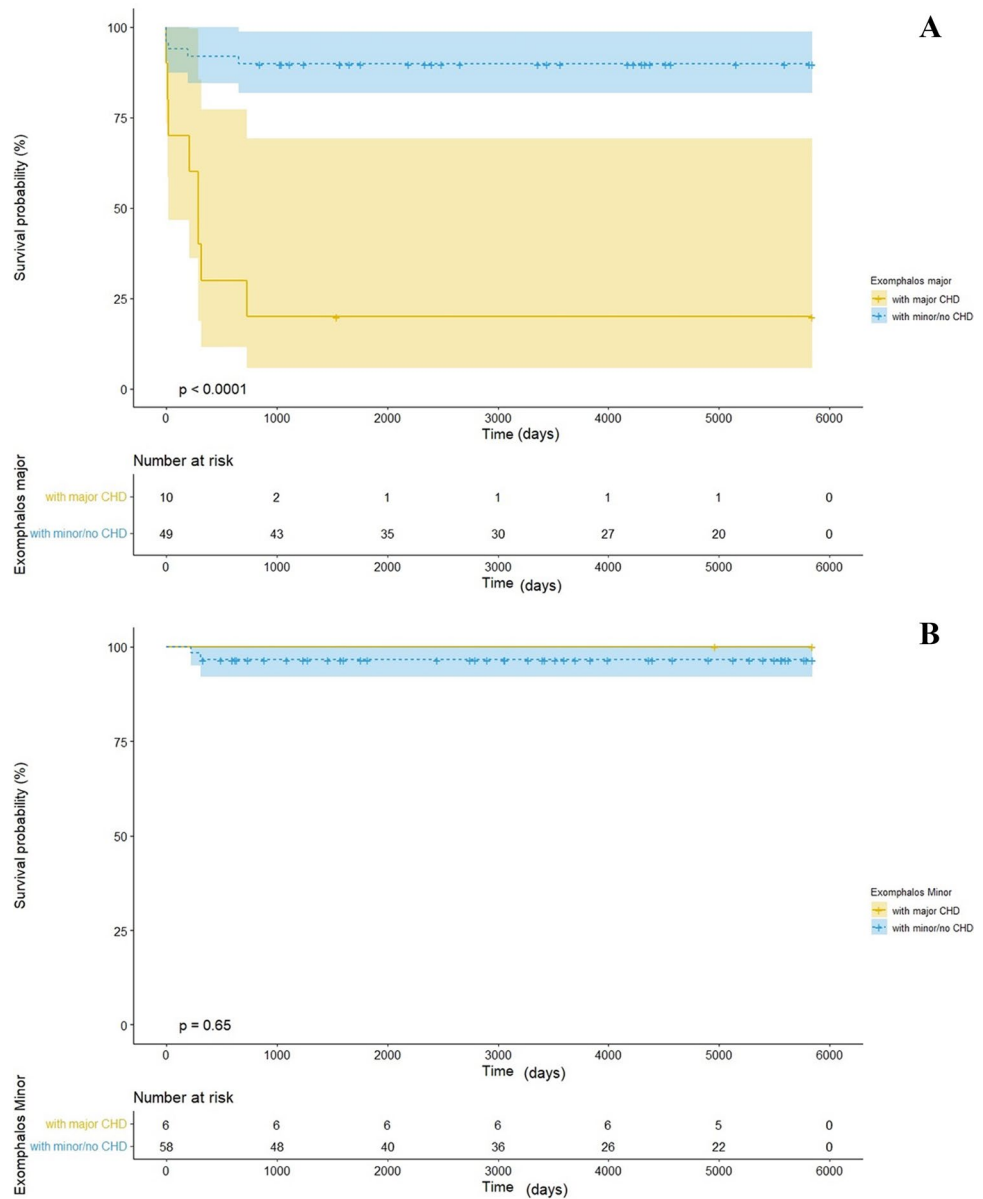
balloon dilatation of RVOT). Prostaglandin infusion therapy was initiated in 4 patient due desaturation episodes.

Eight out of the 10 (80%) patients in this group died. Liver was present in the exomphalos sac in 3/8 deaths. All deaths required pre-intervention MV or prolonged MV for pulmonary hypoplasia. In contrast, the two survivors did not require MV. One of the survivors had ExoMaj repaired on first day of life, then underwent VSD closure at 5 weeks. The other survivor had DORV repaired at 4 weeks followed by ExoMaj repair at 3 years. Only two patients had no comorbidity. Of the two survivors, one had mild developmental delay on most recent follow-up.

Outcomes of ExoMaj with minor or no CHD

Overall mortality in ExoMaj with minor or no CHD was 5/49 (10%). Liver was present in the exomphalos sac in 1/4 deaths. None of the patients in this group were ventilated. Causes of death were sepsis, ruptured exomphalos, severe multi-organ failure, and hypoxic-ischaemic encephalopathy.

Extracardiac anomalies were found in 3/5 patients that died and included hydronephrosis, undescended testicles and hypoxic-ischaemic encephalopathy. Genetic testing was performed in 2/5 children and was normal.
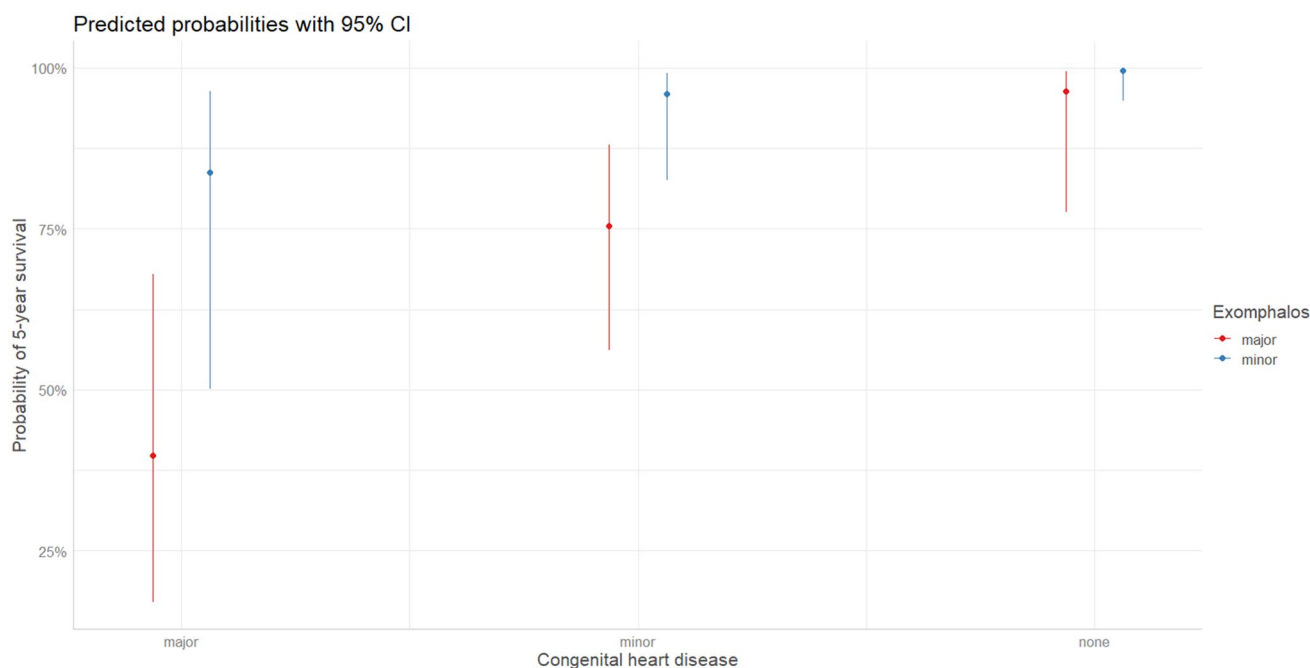
Fig. 3 Model predictions showing probabilities for 5-year survival with 95% confidence intervals for the two variables of interest (ExoMaj and ExoMin)

Outcomes of ExoMin

There were only 2/64 (3%) deaths in this group, both had minor CHD. The first patient had small muscular VSD, died of severe combined immunodeficiency and end stage liver disease. The second had ductus arteriosus (PDA), died of sepsis. None of the patients in this group were ventilated.

Discussion

This study describes the significant mortality associated with EMCHD. To the best of our knowledge, this is the largest series describing the outcome of patients with exomphalos and associated CHD.

Our series was not far from the previously reported results with just over half of our patients having CHD associated with exomphalos [8, 9]. It would not be surprising if associated major CHD led to higher mortality and morbidity, however, a recent retrospective 10-year surgical series by Rees et al. reported that operative outcomes for exomphalos were not affected by the presence of a cardiac defect [3]. Our findings differ to those of Rees with much poorer outcome in the group with EMCHD.

Differences in the type of the CHD associated with ExoMaj may have contributed to the differences in the outcomes between the 2 studies. In the study reported by Rees et al., the cardiac morphology was mainly ASDs, VSDs or PDAs, whereas our group consisted mainly of right heart lesions with reduced pulmonary blood flow and associated pulmonary hypoplasia. Six out of the eight patients who died in our group with EMCHD were of this type of lesion. Prostaglandin infusion therapy was initiated for desaturation episodes in 4 patients as it was not always clear to the clinicians whether desaturation was caused by lung abnormality or the congenital heart defect. In reality, it was most likely a combination of both. Differences in the type of the CHD associated with ExoMaj may have contributed to the differences in the outcomes between the 2 studies.

It is pertinent to emphasise that, although the proportion of major CHD was only slightly different between ExoMaj and ExoMin groups (17% versus 9%), the spectrum of these major CHD differs significantly between the two exomphalos group. The ExoMaj group tend to have more right sided heart lesions with reduced pulmonary blood flow and need for multiple interventions, whereas, the ExoMin group show more of septation defects such as ASDs and VSDs or aortic coarctation which were amenable to single-staged corrective surgery.

The need for pre-intervention MV or prolonged MV and lung hypoplasia appears to be possibly associated with mortality in our group. Rees et al. [3] did not report how many of their cohort required MV prior to intervention, although one patient treated conservatively with pulmonary hypoplasia, died of respiratory distress syndrome. There may also have been selection bias, with some ventilator dependent patients

being excluded. Patients who died in our EMCHD cohort required MV/ prolonged MV prior to intervention. In our opinion, this is may be the main factor contributing to the high mortality in our group of patients as both ExoMaj or major CHD (in isolation) are amenable to complete repair with good outcomes.

Several explanations for pulmonary insufficiency in patients with ExoMaj have been proposed such as (a) impaired diaphragmatic development [20], (b) the marked difference in chest configuration in patients with ExoMaj compared to other abdominal wall defects [21], and (c) increased abdominal pressure and diaphragmatic elevation following early surgical repair [22]. It has also been suggested that infants with anterior abdominal wall defects may have impaired antenatal lung growth [23]. Our study highlights that; babies with EMCHD die from a combination of co-morbidities. They are a complex group of patients, with multi-organ involvement including not just the heart, but also abdominal wall defect and lung hypoplasia; although CHD is an important risk factor, it is likely that the combination of co-morbidities such as pulmonary hypoplasia and need for prolonged MV contribute to mortality.

Cardiac surgical intervention in neonates with reduced pulmonary blood flow carries high risk [24–26]. Transcatheter procedures such as RVOT stenting is considered the first-line treatment for selected patients with severe RVOT obstruction as an alternative to surgical shunt [27]. In the EMCHD, attempts to improve the pulmonary blood flow by balloon dilatation or stenting of the RVOT were performed with technical success, but did not significantly affect the ultimate outcome. It became clear to us that there is a degree of respiratory compromise in this group of patients contributing to desaturation and ventilator dependence, and the causes of desaturation was not solely due to reduced pulmonary blood flow.

Management of ExoMaj continues to present a problem, with no consensus on optimal treatment and each method having challenges [28]. It can be more challenging if it is associated lung hypoplasia, major CHD or other anomalies. Conservative management of ExoMaj allows cardiac intervention to take place prior to exomphalos repair. One of the 2 survivors with EMCHD had exomphalos repaired first, followed by repair of CHD. Therefore, it could be argued, that for those who do not have pulmonary hypoplasia or did not need MV, there might be some benefit of primary repair of the ExoMaj allowing patients to grow to the appropriate age and weight for cardiac repair. It is also possible that intensive care and ventilation strategies might have changed over time, and with advance in surgical managements, our results could have been different.

In summary, despite the adequate cardiac palliation for patients with EMCHD, the outcome remains very poor. Right-sided heart lesions with reduced pulmonary blood flow and, possibly pulmonary hypoplasia and secondary pulmonary hypertension requiring long-term respiratory support seem to be the main predicting factor for early mortality in this group of patients [29, 30]. We found particularly poor outcomes in those patients with EMCHD who needed MV/ Prolonged MV prior to cardiac intervention.

This study has some limitations. It is retrospective, single-centre study which is subject to lack of generalisability, selection bias, and a requirement of a large data collection period to get reasonable sample size for analysis. We suggest future studies are prospective and multi-institutional. Some data was not available to perform full analysis and comparison of outcomes, for example we could not find documentation of echocardiograms for some patients which led us to consider them as either normal or minor CHD. We were also not able to find any patient with exomphalos between the years 1991 and 1997. In addition, we could not conduct analysis of some outcomes such as presence type of genetic testing as we were not able to identify the exact tests done. Finally, multivariable regression analysis that included other variables of interest was not possible to perform due to missing data as well as limited events and high number of variables to be analysed. A large-scale registry data with thousands of patients may be able to analyse the effect of other important possible contributors such as birth weight, gestation, genetics and other associated congenital anomalies.

Conclusion

The association of EMCHD is rare, difficult to manage. Despite intensive multidisciplinary input and best attempts, EMCHD was associated with high mortality. The most significant findings in our series were of possible association of the poor outcomes with right heart anomalies, and pulmonary hypoplasia especially if pre-intervention MV is required. This is an important consideration for antenatal and postnatal counselling.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Springett A, Draper ES, Rankin J et al (2014) Birth prevalence and survival of exomphalos in England and wales: 2005 to 2011 birth defects. Res A Clin Mol Teratol 100(09):721–725. https://doi.org/10.1002/bdra.23301

2. Lawrence L, Gavens E, Reda B, Hill T, Jester I, Lander A, Soccorso G, Pachl M, Gee O, Singh M, Arul GS (2021) Exomphalos major: conservative management using Manuka honey dressings and an outreach surgical nursing team. J Pediatr Surg 56(8):1389–1394. https://doi.org/10.1016/j.jpedsurg.2021.01.026

3. Rees CM, Tullie L, Pierro A, Kiely E, Joe I et al (2018) Primary versus staged closure of exomphalos major: cardiac anomalies do not affect outcome. Eur J Pediatr Surg 28:279–284. https://doi.org/10.1055/s-0037-1603088

4. Groves R, Sunderajan L, Khan AR, Parikh D, Brain J, Samuel M (2006) Congenital anomalies are commonly associated with exomphalos minor. J Pediatr Surg 41(2):358–361. https://doi.org/10.1016/j.jpedsurg.2005.11.013

5. Christison-Lagay ER, Kelleher CM, Langer JC (2011) Neonatal abdominal wall defects. Semin Fetal Neonatal Med 16(03):164–172. https://doi.org/10.1016/j.siny.2011.02.003

6. Gilbert WM, Nicolaides KH (1987) Fetal omphalocele: associated malformations and chromosomal defects. Obstet Gynecol 70(04):633–635

7. Yazbeck S, Ndoye M, Khan AH (1986) Omphalocele: a 25-year experience. J Pediatr Surg 21(09):761–763

8. Gibbin C, Touch S, Broth RE, Berghella V (2003) Abdominal wall defects and congenital heart disease. Ultrasound Obstet Gyneco 21:334–337. https://doi.org/10.1002/uog.93

9. Tulloh RM, Tansey SP, Parashar K, De Giovanni JV, Wright JG, Silove ED (1994) Echocardiographic screening in neonates undergoing surgery for selected gastrointestinal malformations. Arch Dis Child Fetal Neonatal Ed 70(3):F206–F208. https://doi.org/10.1136/fn.70.3.F206

10. Charlesworth P, Ervine E, McCullagh M (2009) Exomphalos major: the Northern Ireland experience. Pediatr Surg Int 25(1):77–81. https://doi.org/10.1007/s00383-008-2292-8

11. Rijhwani A, Davenport M, Dawrant M (2005) Definitive surgical management of antenatally diagnosed exomphalos. J Pediatr Surg 40:516–522. https://doi.org/10.1016/j.jpedsurg.2004.11.028

12. Wakhlu A, Wakhlu AK (2000) The management of exomphalos. J Pediatr Surg 35:73–76. https://doi.org/10.1016/s0022-3468(00)80017-2

13. Tsakayannis DE, Zurakowski D, Lillehei CW (1996) Respiratory insufficiency at birth: a predictor of mortality for infants with omphalocele. J Pediatr Surg 31:1088–1090. https://doi.org/10.1016/s0022-3468(96)90093-7

14. Sakonido K, Farmer I, Ali K et al (2016) Outcomes of antenatally diagnosed infants with exomphalos. Arch Dis Child 101:A244–A245

15. Sokonido K, Ali K, Farmer I et al (2018) Mortality and short-term morbidity in infants with exomphalos. Pediatr Int 5:438–441. https://doi.org/10.1136/archdischild-2016-310863.407

16. Marshall J, Salemi JL, Tanner JP et al (2015) Prevalence, correlates, and outcomes of omphalocele in the United States, 1995–2005. Obstet Gynecol 126(2):284–293. https://doi.org/10.1097/AOG.0000000000000920

17. Sauthier M, Rose L, Jouvet P (2017) Pediatric prolonged mechanical ventilation: considerations for definitional criteria. Respir Care 62(1):49–53. https://doi.org/10.4187/respcare.04881

18. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

19. RStudio Team (2020). RStudio: integrated development environment for R. RStudio, PBC, Boston, MA http://www.rstudio.com/.

20. Argyle JC (1989) Pulmonary hypoplasia in infants with giant abdominal wall defects. Pediatr Pathol 9:43–55. https://doi.org/10.3109/15513818909022331

21. Hershenson MB, Brouillette RT, Klemka L et al (1985) Respiratory insufficiency in newborns with abdominal wall defects. J Pediatr Surg 20:348–353. https://doi.org/10.1016/s0022-3468(85)80217-7

22. Nakayama DK, Mutich R, Motoyama EK (1992) Pulmonary dysfunction after primary closure of an abdominal wall defect and its improvement with bronchodilators. Pediatr Pulmonol 12(3):174–180. https://doi.org/10.1002/ppul.1950120309

23. Thompson PJ, Greenough A, Dykes E, Nicolaides KH (1993) Impaired respiratory function in infants with anterior abdominal wall defects. J Pediatr Surg 28(5):664–666. https://doi.org/10.1016/0022-3468(93)90026-H

24. Van Arsdell GS, Maharaj GS, Tom J et al (2000) What is the optimal age for repair of tetralogy of Fallot? Circulation 102(19 Suppl 3):III123–III129. https://doi.org/10.1161/01.cir.102.suppl_3.iii-123

25. Williams JA, Bansal AK, Kim BJ et al (2007) Two thousand Blalock-Taussig shunts: a six-decade experience. Ann Thorac Surg 84:2070–2075. https://doi.org/10.1016/j.athoracsur.2007.06.067 (**discussion 2070–5**)

26. Petrucci O, O'Brien SM, Jacobs ML et al (2011) Risk factors for mortality and morbidity after the neonatal Blalock-Taussig shunt procedure. Ann Thorac Surg 92:642–652. https://doi.org/10.1016/j.athoracsur.2011.02.030

27. Stumper O, Ramchandani B, Noonan P, Mehta C, Bhole V, Reinhardt Z, Dhillon R, Miller PA, de Giovanni JV (2013) Stenting of the right ventricular outflow tract. Heart 99(21):1603–1608. https://doi.org/10.1136/heartjnl-2013-304155

28. van Eijck FC, Aronson DA, Hoogeveen YL, Wijnen RM (2011) Past and current surgical treatment of giant omphalocele: outcome of a questionnaire sent to authors. J Pediatr Surg 46(03):482–488. https://doi.org/10.1016/j.jpedsurg.2010.08.050

29. Headley BM, McDougall PN, Stokes KB, Dewan PA, Dargaville PA (2001) Left-lung-collapse bronchial deformation in giant omphalocele. J Pediatr Surg 36:846–850

30. Matcovici M, Stoica I, Burhamah W, Alshafei A, Murphy R, Sue T, Muntean A, Awadalla S (2001) Predictors of long-term respiratory insufficiency of exomphalos major. J Pediatr Surg 56(9):1583–1589. https://doi.org/10.1016/j.jpedsurg.2020.12.017