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Congenital diaphragmatic hernia survival in an English regional ECMO center

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ABSTRACT

Introduction Congenital diaphragmatic hernia (CDH) remains a cause of neonatal death. Our aims are to describe contemporary rates of survival and the variables associated with this outcome, contrasting these with our study of two decades earlier and recent reports.

Materials and methods A retrospective review of all infants diagnosed in a regional center between January 2000 and December 2020 was performed. The outcome of interest was survival. Possible explanatory variables included side of defect, use of complex ventilatory or hemodynamic strategies (inhaled nitric oxide (iNO), high-frequency oscillatory ventilation (HFOV), extracorporeal membrane oxygenation (ECMO), and Prostin), presence of antenatal diagnosis, associated anomalies, birth weight, and gestation. Temporal changes were studied by measuring outcomes in each of four consecutive 63-month periods.

Results A total of 225 cases were diagnosed. Survival was 60% (134 of 225). Postnatal survival was 68% (134 of 198 liveborn), and postrepair survival was 84% (134 of 159 who survived to repair). Diagnosis was made antenatally in 66% of cases. Variables associated with mortality were the need for complex ventilatory strategies (iNO, HFOV, Prostin, and ECMO), antenatal diagnosis, right-sided defects, use of patch repair, associated anomalies, birth weight, and gestation. Survival has improved from our report of a prior decade and did not vary during the study period. Postnatal survival has improved despite fewer terminations. On multivariate analysis, the need for complex ventilation was the strongest predictor of death (OR=50, 95% CI 13 to 224, p<0.0001), and associated anomalies ceased to be predictive.

Conclusions Survival has improved from our earlier report, despite reduced numbers of terminations. This may be related to increased use of complex ventilatory strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Survival for babies is dependent on severity of pulmonary hypoplasia.

WHAT THIS STUDY ADDS

⇒ Survival rates are improving despite fewer terminations. Survival without fetoscopic tracheal occlusion (FETO) appears similar to FETO centers. Extracorporeal membrane oxygenation does not significantly affect outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICS OR POLICY

⇒ Survival appears to improve as a result of small incremental improvements.
⇒ Outcomes of FETO should be compared to this benchmark.

INTRODUCTION

In 2003, we published our institutional diaphragmatic hernia (congenital diaphragmatic hernia (CDH)) survival study.[1] In contrast to most studies of that era, we described no improvement in survival over the preceding 10 years, perhaps because we were able to identify deaths occurring in peripheral hospitals and terminations.

We reported total survival of 32% and liveborn survival of 55%. However, we did not analyze the effect of additional cardiac anomalies nor did we attempt to distinguish differing postnatal times of death.

The intervening decades have seen several important innovations in the treatment of CDH. The prognostic utility of the liver position and the fetal lung:head ratio measured on antenatal scan was recognized[2] and subsequently refined.[3] Grading of the risk of mortality has allowed the deployment of novel interventions, such as fetoscopic tracheal occlusion (FETO), with reported improvements in outcomes.[4] However, the utility of such measurements remains dependent on antenatal detection, which may still be relatively low.[5] Extracorporeal membrane oxygenation (ECMO) seems to offer promise,[6] but its precise role remains controversial,[7] and concerns about neurological morbidity persist.[8] Other therapies that have been deployed in the treatment of CDH since our original study include inhaled nitric oxide (iNO)[9] and high-frequency oscillatory ventilation (HFOV).[10]

In the context of these evolving therapies, we were interested in comparing survival in our institution in the last 20 years, contrasting these with our earlier report

and contemporary descriptions of outcomes for this condition.

METHODS

Patients and data collection

We recorded all CDH cases between January 2000 and December 2020. Cases were identified from institutional records, including the regional antenatal service and a dedicated database of CDH repairs. The outcome of interest was survival. We categorized deaths as (1) elective terminations, (2) intrauterine death, (3) postnatal, (4) death without surgical repair, and (5) postnatal death following surgical repair.

Possible explanatory variables were sex, gestation, birth weight, antenatal diagnosis, side of defect, and congenital anomalies. Cardiac anomalies were categorized as (1) atrial septal defect (ASD)/ ventricular septal defect (VSD), (2) patent ductus arteriosus (PDA), or (3) complex. Surgical repair was (1) sutured or (2) prosthetic patch. We did not document defect size during this study, but the use of patches will be a surrogate marker for larger defects. The timing of repair was early (<2 months of age) or late (>2 months of age). We chose this cut-off, recognizing that a proportion of CDH cases manifest no respiratory distress at birth and present later, typically with bowel-related symptoms. We wished to analyze this cohort separately from the cohort presenting with immediate respiratory symptoms.

Complex ventilatory/hemodynamic strategies were (1) iNO, (2) HFOV, (3) ECMO, and (4) prostaglandin E (Prostin, Pfizer).

Statistical analysis

We examined temporal patterns by dividing the period of 21 years into four consecutive 63-month intervals, performing a χ^2 goodness-of-fit test for each outcome. We analyzed the association between survival and explanatory variables using a χ^2 test.

We obtained the OR for survival with predictors using logistic regression. Variables that were significantly associated with survival were then combined in a multivariate model using a forward entry method. Because of the strong collinearity of iNO, HFOV, and Prostin use, we only used iNO in the multivariate model. We hypothesized that there may be differing effects on infants who died prior to repair and therefore performed the analysis twice, with a separate analysis for those who survived to undergo repair.

All analyses were performed using SPSS V.24. Graphs were constructed with SigmaPlot V.13 (Systat, California, USA).

RESULTS

Of 225 cases, 148 (66%) were identified antenatally. After 26 elective terminations and 1 intrauterine death, 198 were liveborn. Birth weight and gestation were greater among survivors (2.9 kg (0.6) vs 2.5 kg (0.8), p<0.0001; 38.0 vs 37.5 weeks, p=0.001) (figure 1). Of the 198 cases, 127 (64%) were male and 154 (78%) had a left-sided defect.

Thirty-nine of 198 (20%) died due to respiratory failure before repair. One child underwent FETO but was delivered less than 48 hours later and survived with no complex ventilation.

Survival

The overall survival was 134 of 225 (60%). Liveborn survival was 134 of 198 (68%), with no sex difference, 85 of 127 (67%) for male cases vs 49 of 71 (66%) for female cases. Of 91 deaths, 27 (30%) occurred antenatally; 39 (43%) occurred postnatally; and 25 (27%) occurred after repair.

Surgical intervention group

Of 159 CDH cases who were repaired, 139 (87%) underwent early repair; 123 (77%) had sutured repair; 36

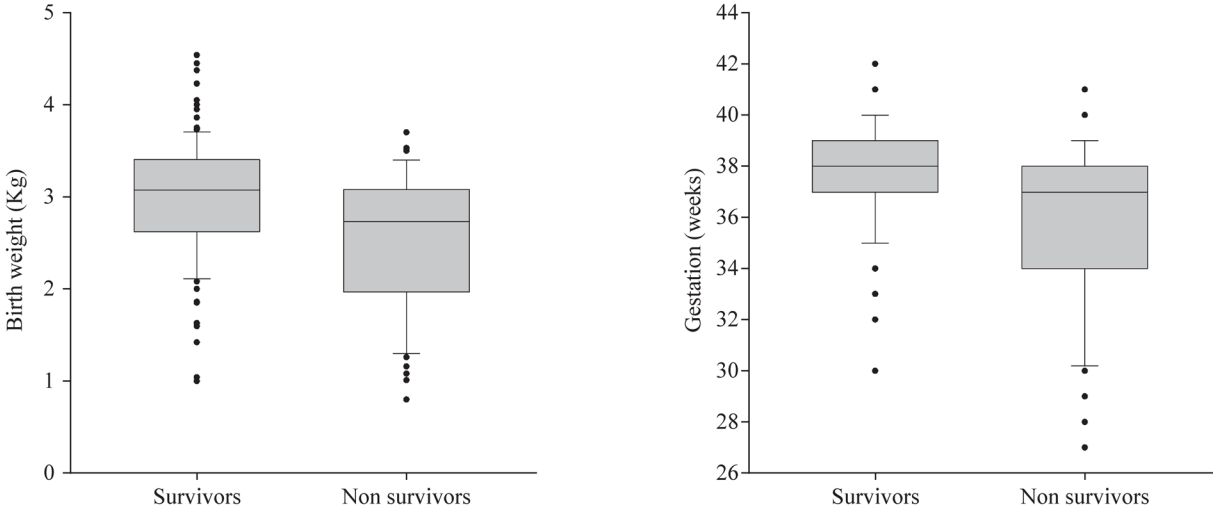

Figure 1 Survival by birth weight (A) and gestation (B).

Table 1 Temporal patterns and frequency of outcomes and explanatory variables over four consecutive time intervals, each of 63 months

Variable	Time period/observed frequency				Expected frequency	χ^2	P value
	1	2	3	4			
Number of cases	52	57	66	50	56	2.7	0.4
Antenatally diagnosed	29	38	46	35	37	4	0.3
Terminations	2	4	15	5	6	15.5	<0.0001
Live birth	52	55	53	48	52	0.5	0.9
Surgical repair	37	42	41	39	40	0.4	0.9
Alive	30	40	35	29	34	2	0.5
HFOV	15	19	26	19	22	3	0.4
iNO	21	19	29	29	22	3	0.4
Prostin	2	15	23	18	14	16	0.001
ECMO	1	0	5	5	5	4	0.2
Significant cardiac anomaly	10	12	14	14	13	1.1	0.7
Isolated non-cardiac anomaly	4	5	4	2	4	1.5	0.6

ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide.

(23%) had prosthetic patches; and 134 (84%) survived. The mean age of cases with early repair was 7 days (SD 8 days) vs 1073 days (SD 1628 days) for cases with late repair. The proportion of survival cases with early repair was 118 of 139 (85%) vs 16 of 20 (80%) for the late repair group (χ^2=1.1, p=0.3) with a mean follow-up of 6 years. Besides, 108 of 123 (88%) cases with sutured repairs survived, while 26 of 36 (72%) cases with patches survived (χ^2=5, p=0.02). We only used one latissimus dorsi patch in a girl whose prosthetic patch had become infected.

Temporal patterns

During the four equal time periods, there was no difference in the observed and expected frequencies of cases diagnosed, antenatal diagnosis, live birth, infants undergoing repair and survival. More terminations occurred in the third period (χ^2=15.5, p<0.0001) (table 1 and figure 2). There was no change in the frequencies of use of HFOV, iNO or ECMO, while the frequency of prostin changed significantly (χ^2=16, p=0.001) (table 1).

Antenatal diagnosis

Of all cases, 148 (66%) had antenatal diagnosis and 77 (34%) had normal antenatal scan and postnatal diagnosis. Of the 198 live births, 68 of 121 (56%) antenatal diagnosed cases survived, and 66 of 77 (86%) postnatal diagnosed cases survived (χ^2=18, p<0.0001) (figure 3).

Following repair (159 cases), antenatal diagnosis remained a predictor of death, with survival in 68 of 87 cases diagnosed antenatally (78%) vs 66 of 72 cases diagnosed postnatally (92%) (χ^2=5, p=0.02).

Antenatal diagnosis was strongly associated with HFOV (χ^2=30, p<0.001), iNO (χ^2=17, p<0.001), ECMO (χ^2=4, p=0.03), and Prostin use (χ^2=21, p<0.0001) (figure 3).

Left-sided defects were significantly more likely to be antenatally diagnosed (118 in 170 (69%) vs 24 in 49 (49%); χ^2=10.2, p=0.016). Two cases of bilateral defects were also diagnosed antenatally.

The adverse survival of the right side worsened if diagnosed antenatally. Only 5 out of 18 (28%) live births with a antenatal diagnosis of right-sided defect survived vs 63 out of 103 (61%) live births with an antenatal diagnosis of left-sided defect (χ^2=7, p=0.008).

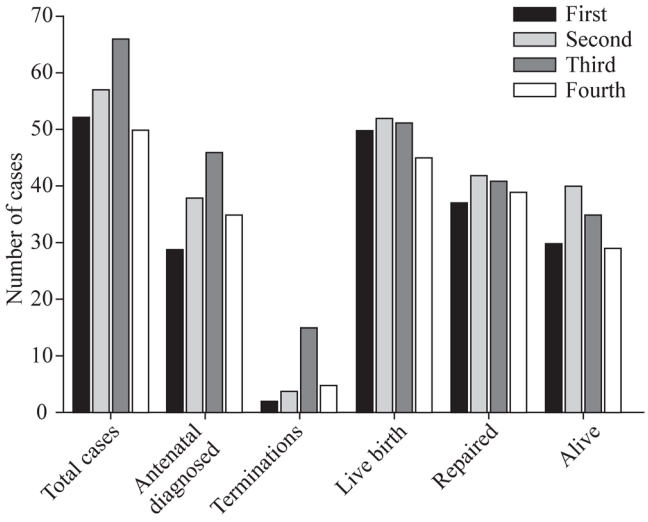

Figure 2 Temporal patterns of cases, antenatal diagnosis, terminations, live birth, repairs and survival during four consecutive periods of 63 months for the duration of the study.

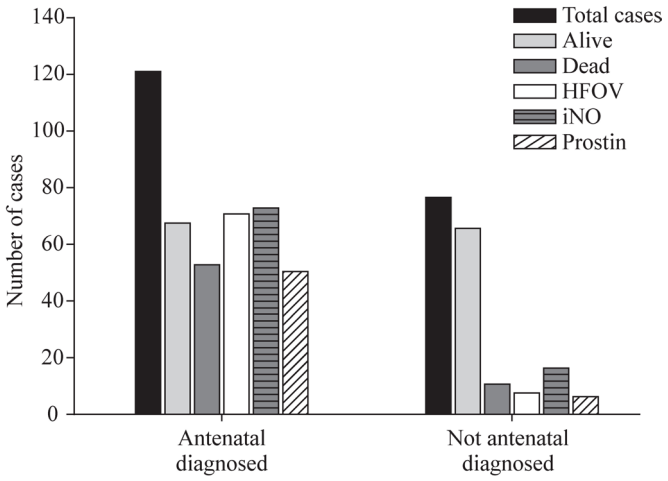

Figure 3 Incidence and association of antenatal diagnosis with outcomes. HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide.

Terminations

We found only a weak correlation between the annual termination rate and the annual postnatal survival rate (R^2=0.23, p=0.025).

Associated anomalies

We also discovered that of the 225 cases, 21 (9%) had isolated non-cardiac anomaly, and 52 (23%) had an isolated cardiac anomaly.

Of the 198 live births, 115 (58%) cases had echocardiogram; 43 (22%) had either an ASD or a VSD; 37 (19%) had an isolated PDA; and 7 (4%) had a more complex cardiac anomaly. Of the 83 cases that did not have echocardiogram, 62 (75%) were alive and could be assumed to have no significant cardiac anomaly. Of the remaining 21 cases, 16 died before repair, with 12 dying either on the day of birth or on the following day. Five of the 198 cases (3%) died without cardiac assessment after repair.

We assessed the influence of cardiac anomalies on survival by combining the ASD/VSD group with the more complex anomalies to give a group of 50 with a significant cardiac anomaly. Postnatal survival of cases with either no cardiac anomaly, an ASD/VSD, a more complex cardiac anomaly, or a PDA was the same (χ^2=1.9, p=0.5).

Twenty-one babies had an additional non-cardiac anomaly, of whom 6 cases (29%) survived, while 15 (71%) died (χ^2=17, p<0.001). Of the 21 babies with an additional anomaly, a total of 17 (81%) were diagnosed antenatally, compared with 139 of 214 babies (65%) with no additional anomaly (χ^2=2.1, p=0.1). Children were not more likely to be diagnosed antenatal if there was an associated anomaly.

The adverse effect of additional anomalies was specific to non-cardiac anomalies. Thirty (60%) of 50 infants with an isolated cardiac anomaly survived vs 104 (70%) of 148 infants without an isolated cardiac anomaly (χ^2=1.8, p=0.2).

High-frequency ventilation or nitric oxide or Prostin administration

Of the 198 live births, 76 cases (38%) underwent HFOV, and 90 (45%) received iNO (table 2). The two strategies were used concurrently in most cases (n=73). Seventeen received iNO without HFOV, and 6 underwent HFOV without iNO. Both were strongly associated with death. We found that 35 (39%) of 90 cases who received iNO survived (χ^2=62, p<0.0001), while 27/79 (19%) of those who underwent HFOV survived (χ^2=67, p<0.0001) (table 2).

Table 2 Univariate analysis of variables related to survival of live births

Variable	Frequency	Death in the presence of variable (%) or mean (SD) among non-survivors for continuous data, n (%)	Death in absence of variable (%) or mean (SD) among survivors for continuous data, n (%)	OR of death (95% CI)	P value
Antenatal diagnosis	121/198	53/121 (44)	11/77 (14)	4.6 (2.2 to 9.7)	<0.0001
Right-sided defect	43/198	19/43 (44)	45/155 (29)	1.9 (0.9 to 3.8)	0.06
Isolated additional anomaly	15/198	9/15 (60)	55/183 (30)	3.4 (1.1 to 10.2)	0.02
Isolated cardiac anomaly	50/198	20/50 (40)	44/148 (30)	1.5 (0.8 to 3.0)	0.2
PDA	61/198	18/61 (29)	46/137 (34)	0.8 (0.4 to 1.5)	0.5
High-frequency ventilation	79/198	52/79 (66)	12/119 (10)	17 (8 to 36)	<0.0001
Nitric oxide	90/198	55/90 (61)	9/108 (8)	17 (8 to 38)	<0.0001
ECMO	11/198	7/11 (64)	57/187 (31)	4 (1.1 to 14)	0.03
Prostin	58/198	30/50 (52)	34/140 (24)	3 (1.7 to 6)	<0.0001
Birth weight (kg)		2.49 (0.8)	2.99 (0.6)	0.4 (0.2 to 0.6)	<0.001
Gestation (weeks)		35 (5)	37 (2)	0.82 (0.7 to 0.9)	<0.001

ECMO, extracorporeal membrane oxygenation; PDA, patent ductus arteriosus.

Table 3 Univariate analysis of variables related to survival of infants who survived to undergo repair

Variable	Frequency	Death in the presence of variable or mean (SD) among non-survivors for continuous data, n (%)	Death in the absence of variable or mean (SD) among survivors for continuous data, n (%)	OR of death (95% CI)	P VALUE
Antenatal diagnosis	87/159	19/87 (22)	6/78 (8)	3 (1 to 8)	0.02
Right-sided defect	34/159	10/34 (29)	15/125 (12)	3 (1.2 to 7.0)	0.02
Defect patched	36/159	10/36 (28)	15/123 (12)	3 (1.1 to 6.8)	0.03
Isolated additional anomaly	9/159	3/9 (33)	22/150 (15)	3 (0.6 to 12.0)	0.1
Isolated cardiac anomaly	39/159	9/39 (23)	16/120 (13)	1.9 (0.7 to 4.8)	0.1
PDA	49/159	6/49 (12)	19/110 (17)	0.6 (0.2 to 1.7)	0.4
HFOV	43/159	16/43 (37)	9/116 (8)	7 (2.8 to 17.0)	<0.0001
iNO	54/159	19/54 (35)	6/105 (6)	9 (3.3 to 24.0)	<0.0001
Prostin	41/159	13/41 (32)	12/118 (10)	4 (1.6 to 10.0)	0.002
ECMO	9/159	5/9 (56)	20/150 (13)	8 (2 to 32)	0.003
Birth weight		2.3 (0.8)	2.9 (0.7)	0.3 (0.17 to 0.6)	<0.0001
Gestation		35 (3)	37 (2)	0.7 (0.6 to 0.8)	<0.0001

ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; PDA, patent ductus arteriosus.

Fifty-eight of 198 live births (29%) received Prostin, which was also associated with death (30 of 58 (52%) vs 34 of 140 (24%); χ^2=14, p<0.0001) (table 2).

Extracorporeal membrane oxygenation

Eleven of 198 (6%) live births underwent ECMO, with 4 of 11 (36%) surviving vs 130 of 187 (69%) of those who did not undergo ECMO (χ^2=5.2, p=0.02) (table 2). Of the four survivors, one had a neurological deficit, compared with 5 of 130 (3%) of those who did not undergo ECMO (exact test p=0.1).

Six of 11 cases (55%) required emergency laparotomy or thoracotomy due to complications (usually bleeding), with 4 dying, vs 5 of 187 (3%) of non-ECMO infants (χ^2=40, p<0.0001).

Seven repairs were performed while on ECMO: four cases died and two of the three survivors were neurologically impaired. Three had repair prior to ECMO, and one required ECMO after repair.

Only 1 in 11 children (9%) were alive after ECMO, did not require emergency surgery, and had no neurological deficits.

Logistic regression analysis of explanatory variables

Univariate analysis showed the following variables to be associated with mortality: antenatal diagnosis; right-sided defects; the use of patch, HFOV, iNO, Prostin and ECMO; birth weight; and gestation (tables 2 and 3). On multivariate analysis, only the use of iNO (p<0.0001) and birth weight (p=0.008) were significantly associated with postnatal survival (table 4). For infants who survived to undergo repair, only iNO (p=0.002) (and therefore HFOV and Prostin), antenatal diagnosis (p=0.047), and the side of the defect (p=0.04) were significant (table 5).

DISCUSSION

In the contemporary era, in an English regional center, we describe overall survival for the anomaly of CDH of 60%, postnatal survival of 68%, and postrepair survival of 84%. The following variables are individually associated with significantly poorer survival: lower birth weight, antenatal diagnosis, right-sided defects, non-cardiac-associated anomalies, requirement for patch repair, and use of complex ventilatory/hemodynamic strategies. Taken in combination, only lower birth weight and the need for complex ventilatory/hemodynamic strategies remained significant predictors of death. Our outcomes reflect our management practices, which may differ from those of other institutions.

Table 4 Multivariate analysis of variables related to survival of live births.

Variable	OR of death (95% CI)	P value
Antenatal diagnosis	3 (0.9 to 10)	0.06
iNO	53 (13 to 224)	<0.0001
Isolated additional anomaly	3 (0.5 to 21)	0.2
Prostin	0.6 (0.2 to 1.6)	0.3
ECMO	3 (0.6 to 12.0)	0.1
Birth weight	0.3 (0.1 to 0.7)	0.008
Gestation	0.5 (0.7 to 1.1)	0.5

ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide.

Table 5 Multivariate analysis of variables related to survival of infants who survived to undergo repair

Variable	OR of death (95% CI)	P value
Antenatal diagnosis	9 (1-83)	0.047
Right-sided defect	5 (1-26)	0.04
Defect patched	0.4 (0.1 to 1.926)	0.3
Isolated cardiac anomaly	1.4 (0.3 to 5)	0.6
iNO	23 (3 to 180)	0.002
Prostin	2.2 (0.4 to 10)	0.4
ECMO	3 (0.6 to 18)	0.1
Birth weight	0.3 (0.7 to 1.5)	0.1
Gestation	0.8 (0.5 to 1.1)	0.2

ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide.

Defect side and size, associated anomalies and effect of cardiac anatomy

Right-sided defects had poorer survival (54%) than left-sided defects (71%). The poorer survival of patched repairs corroborates studies relating the size of defects to survival.[11] Others report poorer survival with patches.[12] There are claims of improved outcome with high rates of patch,[13] but survival was identical to our 84% with a conservative approach to patch. The use of patches is a surrogate marker for larger defects in our series. This will not be true for centers that repair most defects by patch. We report elsewhere the association between patch use and recurrence.[14]

An additional non-cardiac anomaly decreases the probability of survival but cardiac anomalies do not. This corroborates the findings of our earlier report.[1]

Survival correlates with levels of beta natriuretic peptide, indicative of heart strain.[15] Theoretically, therefore, cardiac defects that decrease pulmonary hypertension might offer survival advantages, but we found that neither ASD or VSD nor PDA improved survival. Others have noted that even with suprasystemic pulmonary pressures, atrial level shunting is left to right.[16] We lack depth of information about pressures and flow directions. Prostin was associated with a poorer outlook, as it was used selectively in the presence of significant pulmonary hypertension or signs of right heart strain.

Antenatal diagnosis

Among live births, those antenatally diagnosed had worse survival (56% vs 86%). Antenatal diagnosis also predicted the need for HFOV, iNO, and Prostin, all strongly associated with mortality. While it might be thought that antenatal diagnosis would be more likely in the context of multiple anomalies; in fact, the excess mortality among antenatal cases was not because of additional anomalies, which is a separate, independent predictor of mortality.

Comparison with previous studies

There was a weak relationship between the termination rate and postnatal survival. We could not reproduce the association between the termination rate and postnatal survival in our earlier report.[1] There was no pattern of change with time during the study period.

In the 1990s, we reported an overall survival of 71 of 185 cases (38% vs 60% in the current study), postnatal survival of 71 of 129 live births (55% vs 68%), and post-repair survival of 71 of 111 cases (63% vs 84%). All three indices improved from our earlier report.[1]

We report postrepair survival of 144/169 (84%) . In a study of late mortality, ventilation beyond 30 days and ECMO predicted death,[17] agreeing with our multivariate analysis of postrepair mortality, where complex ventilation remained the strongest predictor of death.

Compared with our earlier report, improved rates of survival are accompanied by increasing rates of antenatal diagnosis (52%–66%) and decreased terminations (24%–12%). This may be explained first by the strong association between antenatal diagnosis and complex ventilatory strategies and second by our increased use of these strategies. In our earlier study,[1] 12 of 64 cases (19%) received iNO vs 90 of 198 cases (45%) in the current study, while 13 of 66 cases (20%) underwent HFOV previously vs 76 of 198 cases (40%).

The Congenital Diaphragmatic Hernia Study Group (CDHSG) suggests that survival has improved over the same period.[18] Improved survival after ECMO was also reported.[19] Our liveborn survival of 68% resembles the 70% of a multi-institutional German study[20] and a Californian 72%.[21] A Danish study of population size identical to ours reported 80% survival with no ECMO use.[12] Our 56% survival among antenatal diagnosed cases, and 86% survival with no antenatal diagnosis resembles the CDHSG 65% and 83%.[22] A UK audit described 1-year survival of 69%, with no change in disease incidence or survival.[23] While this equates to our postrepair survival of 84%, we are skeptical that neonates who died before repair are captured by hospital episode statistics, as the authors concede. Our 30-day postoperative mortality of 3% is similar to the UK figure of 4%.

The Antenatal CDH registry group (ACDHRG) described right-sided defects and lower gestation as predictors of death, as we did.[3] We did not subcategorize left-sided defects by liver position and did not measure the fetal lung:head circumference ratio (LHR). Others comment on variable use, difficulties in standardization, and reproducibility of these measurements.[24 25] Although the fetal LHR is proposed as being prognostic, it should be noted that the area under the curve of the receiver operator characteristic is only 0.76, indicative of only a 'fair' test.[3] There remains a considerable overlap between survivors and non-survivors when using the fetal LHR. We note other groups proposing further refinements to the use of antenatal measurements,[26] suggesting that we may yet have to arrive at a definitive antenatal prognostic test.

There are conflicting reports on the significance of liver position for left-sided defects, with the same group suggesting that it is[27] and is not[3] prognostic. The overall survival for the ACDHRG infants with left-sided defects was 126 of 339 (62%), the same as our live-birth survival of 63 of 103 (61%). The same group reported 11 of 25 (44%) survival cases in those with right-sided defects, while our study showed 5 of 18 (28%) survival cases. However, the ACDHRG selected fetuses with isolated defects, while we reported all cases.

Fetoscopic tracheal occlusion

In a randomized trial, FETO was shown to reduce the risk of death among high-risk fetuses with isolated left-sided defects, with survival of 40% compared with 15% in a control group.[4] However, the same authors reported a population cohort when all patients with CDH were included and FETO was applied, with survival of 62%, which was lower than our 68% with no FETO.[28] A large proportion of the babies in the population-based study underwent FETO, 77 of 162 (47%), with 36 surviving. Another contrast is that 78% of patients received patch compared with our 23%. It is difficult to reconcile these survival figures. Clearly, there has been no attempt to distinguish high-risk fetuses in our series, and these babies must be present. However, survival is better than where FETO is liberally applied.

Applying FETO to right-sided defects, results showed that 44 of 116 (38%) survived, but the controls had particularly poor survival of 3 of 26 (12%).[29] We reported survival of 4 of 15 (27%) patients with no FETO.

Ventilatory strategies

The association between iNO, HFOV, Prostin, and death indicates that these therapies were applied to the sickest babies. We suggest the failure of others to demonstrate this indicates the therapies being applied to babies who could have survived without their use.[30 31] Some reports use iNO in 70% of cases,[32] which seems difficult to reconcile with our figure of 45% of cases requiring iNO.

Extracorporeal membrane oxygenation

ECMO survival (52%) is identical to the Extracorporeal Life Support Organization registry[33] and higher than the 36% survival where high risk was defined by the lowest achievable $paCO_2$.[34] Among babies who underwent ECMO in our series, emergency surgery for complications was 38%, and neurological deficits were 60%, indicating the complexity and risks of this therapy. We are one of five UK centers offering ECMO, yet only 6% of inborn babies receive ECMO, with a further 10 referred from the UK and Eire. A UK audit reported that 4% of patients were offered ECMO between 2003 and 2016.[23] An Austrian study reported –1/3 one third of patients receiving ECMO, but survival was identical to ours.[35] ECMO was deployed in 28% of patients in California, again with survival similar to ours.[21] In contrast, an American survey reported 13% of patients undergoing ECMO, with postrepair 30-day mortality of 9%.[36] Wide variations in ECMO use and survival have been documented,[37] implying ECMO use among infants who could survive without ECMO. Given the incidence of neurological damage, this would be a significant error.[38 39] There are reports of high survival of patients with no ECMO.[12] We do not believe that ECMO will significantly reduce mortality in the UK.

Volume: outcome

We repaired an average of eight cases per annum. A systematic review showed that while there is no accepted definition of high volume, by most standards, we are a high-volume center.[40] A UK study indicated that more than six repairs would be high volume.[23] The median number of repairs in Californian centers was seven,[21] with a survival advantage toward higher volume. Because of our numbers of patients and being an ECMO center, it seems unlikely that our findings are explained by lack of experience.

Limitations of this study

Our study suffers from the following limitations. Treatment was in all cases pragmatic and therefore subject to random variation. It is entirely possible that babies might have been allocated to different treatment modalities had differing clinicians been responsible. As we state in our introduction, therapy has changed in the study time period, and willingness to adopt therapies will vary during the study period. We describe contemporary outcomes in an English regional center and accept that these may not be generalizable to other healthcare settings.

Conclusions

We have found that despite fewer terminations, survival has increased. Survival is predicted by birth weight, antenatal diagnosis, need for complex ventilatory/hemodynamic therapies, and non-cardiac anomalies but not cardiac anomalies. Right side and repair by patch are deleterious among those repaired. Overall survival is comparable to centers offering FETO, and ECMO has not significantly reduced mortality.

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