



SURVIVAL RATES OF CONGENITAL DIAPHRAGMATIC HERNIA AND SPECIFIC PREDICTORS OF OUTCOME IN TERTIARY CARE NICU

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KEYWORDS :

Introduction

Congenital diaphragmatic hernia (CDH) accounts for 8% of all major congenital anomalies with an incidence of 1 in 2000 to 4000 births (Doyle & K.P. Lally 2004). It is associated with significant mortality and morbidity (Abdullah et al., 2009). Survival data for CDH are conflicting; a few centers reported 82% to 93% survival rate (Javid et al., 2004; Grushka et al.2009; Mettauer et al., 2009) while others had significantly less figures (54%-56%) (Colvin et al., 2005; Levison et al., 2006). This divergence in survival data has been attributed to case selection bias at single tertiary care institutions because as many as 35% of live-born infants with CDH do not survive to transport resulting in a "hidden mortality" for this condition (Harrison et al., 1978; Colvin et al.; 2005, V.K. Mah et al., 2009). Hidden mortality is referred to patients who die before surgery, either during gestation or shortly after birth and thus are not reported by individual institutions (Harrison et al).

The prognosis of infants with CDH depends on the extent of pulmonary hypoplasia. Despite progress in medical and surgical care, the mortality rate of congenital diaphragmatic hernia remains high. Assessment of short-term outcome is important for comparison between different medical centres.

The primary objective of our study was to evaluate the short-term outcome of infants who were admitted to Nowrosjee wadia maternity hospital (NMWH) and Bai jerbai wadia hospital for children (BJWHC) from January 2013 to December 2015. The secondary goal was to correlate clinical parameters before and soon after birth with the short-term outcome of these infants.

AIMS AND OBJECTIVES

To study the survival rates of Congenital Diaphragmatic Hernia in tertiary care nice.

To review on specific predictors of outcome in congenital diaphragmatic hernia infants.

This is a retrospective study of 30 cases of congenital diaphragmatic hernias hospitalized, monitored and operated during the last 3 years (2013 - 2015) admitted in B J Wadia NICU. The data was collected retrospectively from the admission register and examination of admission files Demographic profile of patient and factors to be evaluated are recorded in study design sheet. All cases were sheeted, the obtained data being included in a large data base and statistically processed using the MS Excel program; when compounding the data base we followed the following parameters for each case:

Data were analysed using SPSS V 19 (Statistical Package for Social Sciences Version 15). Data were given as Mean and SD for numerical data and Number (Percentage) for categorical data. Mann-Whitney U test was used to compare means between 2 groups. Chi square tests and/or Fisher Exact Probability tests were used to compare percentages all statistical tests were 2 tailed. Level of Significance was

taken as P=0.05. NS=No Significant, S= Significant, P=Probability value.

Results

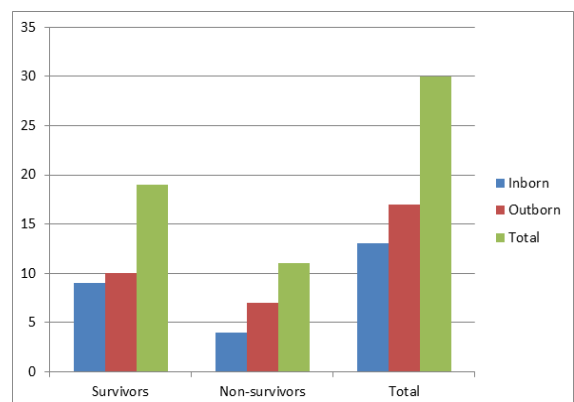
30 cases of Congenital diaphragmatic hernia were admitted to Bai Jerbai Wadia Hospital for Children during the study period of 3 years from January 2013 to December 2015 out of which 13 patients were born in NWMH (inborn) and 17 were referred from outside to BJWHC (outborn).

Demographic & Antenatal characteristics [Table 1]

Table 1: association between demographic and antenatal characteristics and survival

Sr. No.	Demographic & Antenatal characteristics	Survivors (N=19)	Non-survivors (N=11)	P value
1.	Gender Male Female	11 (57%) 8 (73%)	8 (43%) 3 (27%)	0.176
2.	Diagnosis Antenatal Postnatal	8 (67%) 11 (61%)	4 (33%) 7 (39%)	0.150
3.	Hospital of birth Inborn Out born	9 (69%) 10 (59%)	4 (31%) 7 (41%)	0.042*
4.	Mode of delivery NVD Caesarean section	5 (50%) 14 (70%)	5 (50%) 6 (30%)	0.176
5.	Gestation Preterm Term	1 (50%) 18 (64%)	1 (50%) 10 (36%)	0.164
6.	LHR (n=11)	1.278 (7)	0.95 (4)	0.057*

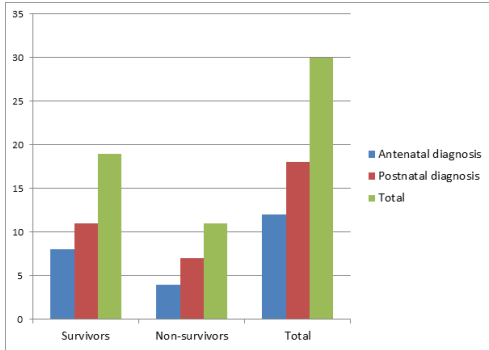
Association between Place of delivery and Survival



Hospital of birth	Survivors	Non-survivors	Total
Inborn	9	4	13
Out born	10	7	17
Total	19	11	30

Demographic characteristics such as place of birth had a statistical significance with all 13 inborn patients having antenatally confirmed diagnosis had a 69% survival rate compared to 59% of out born patients presenting in BJWHC (p=0.042).

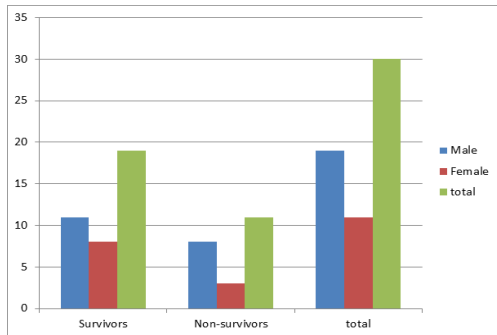
Association between Prenatal diagnosis and Survival



Timing of diagnosis	Survivors	Non-survivors	Total
Antenatal	8	4	12
Postnatal	11	7	18
Total	19	11	30

Of the antenatal characteristics, antenatal diagnosis had marginally better rate of survival though it was not of statistical significance (67% v/s 61% of postnatal diagnosis, p=0.150).

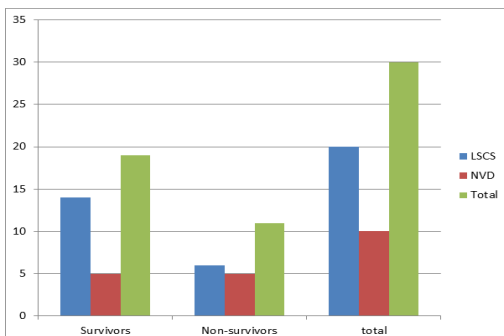
Association between Gender and survival



Gender	Survivors	Nonsurvivors	Total
Male	11	8	19
Female	8	3	11
Total	19	11	30

Majority of patients in our cohort were male babies (69%), with a lower rate of survival, compared to female babies (57% vs 73%, p=0.176) LHR i.e. Lung to head ratio was expectedly on an average higher in survivors (1.276) compared to non survivors (0.9) (p=0.057, CI90%).

Association between Mode of delivery and Survival



Mode of delivery	Survivor	Non-survivor	Total
LSCS	14	6	20
NVD	5	5	10
total	19	11	30

Caesarean section was the preferred mode of delivery in inborn section with almost 76% (10 out of 13) delivered through lscs out of which 70% (7 out of 10) survived and mode of delivery did not affect outcome.

Perinatal characteristics [Table 2]

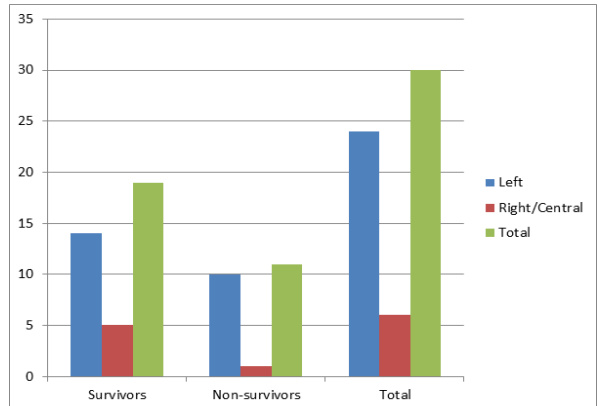
Table 2: association between perinatal characteristics and survival

Sr. No	Perinatal characteristics	Survivors (N=19)	Non-survivors (N=11)	P value
1.	Hernial site			0.440
	Left	14 (58%)	10 (42%)	
	Right/central	5 (83%)	1 (17%)	
2.	Birth weight*	2.862 (2.698 – 3.026)	2.717 (2.588 – 2.846)	0.800
3.	Age at presentation in days*	5.53 (3.3 – 8.7)	2.18 (1.4 – 3.2)	0.328
4.	Severe Pulmonary hypertension**			0.225
	Present	4 (45%)	5 (55%)	
	Absent	15 (84%)	3 (16%)	
5.	Other anomalies			0.574
	Present	3 (50%)	3 (50%)	
	Absent	16 (67%)	8 (33%)	

* Data presented as median (minimum to maximum)

** (n=27) in pulmonary hypertension, data not available for 3 patient

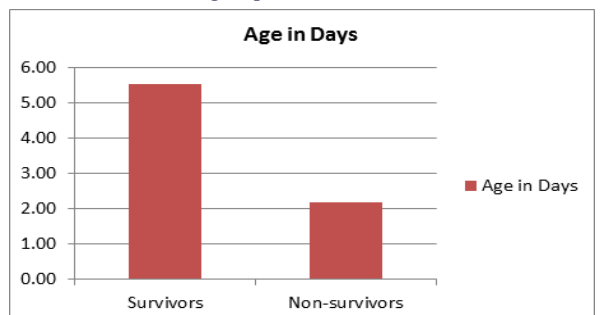
Association between Site of hernia and Survival



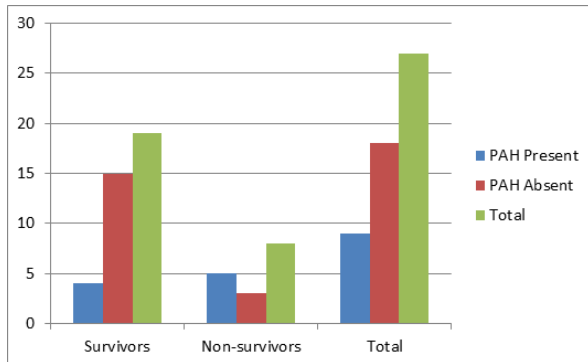
Hernial site	Survivor	Nonsurvivor	Total
Left	14	10	24
Right/Central	5	1	6
Total	19	11	30

With left being most common site of herniation (80%), it had a poorer outcome with 58% compared to 83% survival in right/central tendon herniation (p=0.440).

Association between Age at presentation and Survival



Survivors had a better mean birth weight (2.863 v/s 2.717, non-survivors) and comparatively delayed presentation with a mean age of presentation on 6th day of life. Survival rate was better for those presenting in late neonatal period (80%) which correlated very well with earlier presentation seen in Non-survivor group with almost 81% (9 out of 11) presenting on day1 itself with 55% of them out born (p=0.328).

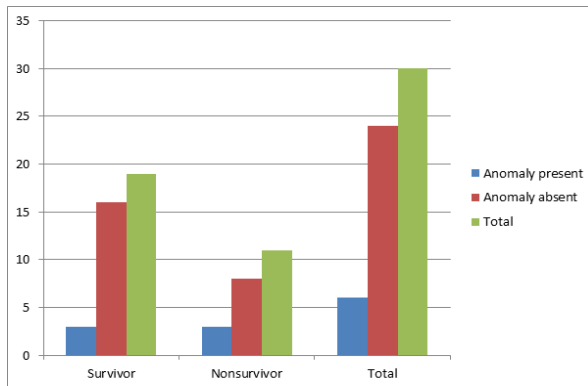


Association between Pulmonary hypertension and survival

Pulmonary hypertension	Survivor	Nonsurvivor	Total
Present	4	5	9
Absent	15	3	18
Total	19	8	27*

* (n=27) in pulmonary hypertension, data not available for 3 patient Echocardiography confirmed presence of moderate to severe pulmonary hypertension was associated with lesser survival (45% v/s 84%, p=0.225), while echocardiography report was not available for 3 patients as they expired within short span of time after presentation.

Association between Related anomalies and Survival



Related anomaly	Survivors	Nonsurvivor	Total
Present	3	3	6
Absent	16	8	24
Total	19	11	30

Congenital anomalies were present in 6 cases (20%) and yielded a 50% survival rate (P = 0.576). These anomalies were musculoskeletal (n=1), cardiovascular (dextrocardia, atrio-ventricular septal defect) (n=1), gastrointestinal (n=4) and craniofacial (n=2) with considerable overlapping, karyotype reports were not available for most of the babies except for one with craniofacial and musculoskeletal deformities which was normal. Isolated CDH survival rate was 66.7%.

Received treatment [Table 3]

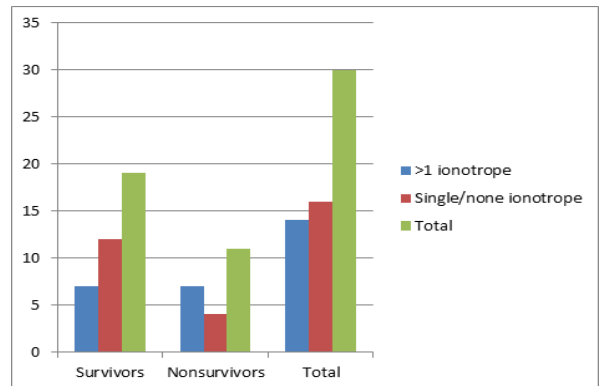
3: association between treatment offered and survival

Sr. no	Treatment received	Survivors (N=19)	Non-survivors (N=11)	P value
1.	Ventilation Conventional Conventional & HFOV	16* (64%) 0	9 (36%) 2 (100%)	0.126

2.	Pulmonary vasodilators# Not given Given	14 (78%) 5 (42%)	4 (22%) 7 (58%)	0.063
3.	Ionotropic support^ (>1) Not given Given	12 (75%) 7 (50%)	4 (25%) 7 (50%)	0.150

* ventilation was never required in 3 of the survivors
pulmonary vasodilators used: Milrinone / sildenafil/ magnesium
^ ionotropes used: dopamine / dobutamine / adrenaline / noradrenaline

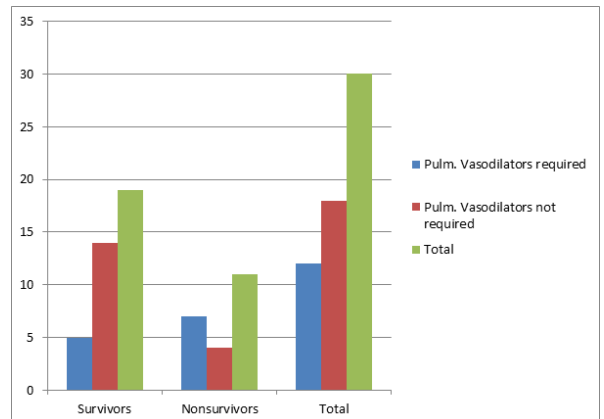
Association between Need for >1 ionotropes and Survival



Ionotrope used >1	Survivors	Nonsurvivors	Total
Given	7	7	14
Not given	12	4	16
Total	19	11	30

Hemodynamic instability to such an extent requiring use of more than one ionotrope correlated very well with lesser survival 50% v/s 75% though statistical significance is debatable (P=0.150).

Association between Need of pulmonary vasodilators and Survival



Pulmonary vasodilators	Survivors	Nonsurvivors	Total
Required	5	7	12
Not required	14	4	18
Total	19	11	30

Considering drug groups only, the necessity to administer pulmonary vasodilators to control the severe pulmonary hypertension was associated with lesser survival rate (42% v/s 78%, p= 0.063, CI 95%). 27 (90%) newborns were intubated either in delivery room or in NICU, paralysed and sedated, while 3 newborns did not require ventilatory support either pre-op or post-op. Goal of ventilation was to maintain pH in the range from 7.35-7.45, pO2 above 80, pCO2 between 35-55, preductal saturations above 85%. Conventional ventilation was the preferred mode of ventilation (90%), while high frequency ventilation was used in 2 patients to prevent respiratory failure when convention ventilation failed, but that too could not alter the course of illness.

70% had a severe GER and required anti-reflux measures including anti-reflux medications. One required Nissen fundoplication with

gastrostomy because of persistent vomiting and inability to gain weight.

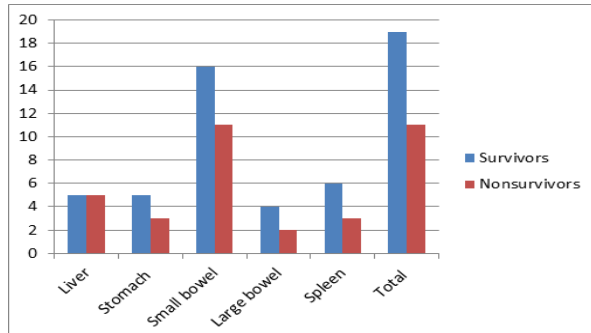
The mean period of ventilation was 8 days (range from 3-43days) and average duration of nicu stay being 22 days (9-55 days). Median for start of feeds was day 14 with full feeds achieved by around day19. Surgical characteristics [Table 4]

Table4: association between surgical characteristics and survival

Sr. No.	Surgical characteristics	Survivors (N=19)	Non-survivors (N=11)	P value
1.	Surgery Performed Not performed#	19 (76%) -	6 (24%) 5 (100%)	0.003*
2.	No. Of organs in chest cavity 1 organ >1 organ	6 (75%) 13 (59%)	2 (25%) 9 (41%)	0.672
3.	Liver Yes No	5 (50%) 14 (70%)	5 (50%) 6 (30%)	0.425
4.	Stomach Yes No	5 (62%) 14 (63%)	3 (38%) 8 (37%)	1.000
5.	Small bowel Yes No	16 (59%) 3 (100%)	11 (41%) -	0.279
6.	Large bowel Yes No	4 (67%) 15 (62%)	2 (33%) 9 (38%)	1.000
7.	Spleen Yes No	6 (67%) 13 (59%)	3 (33%) 8 (41%)	1.000

#Note 5 patients could not be stabilised pre-operative.

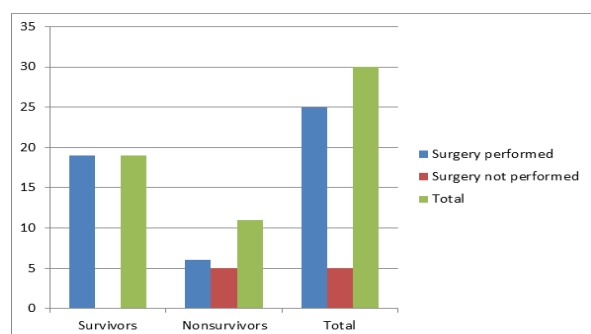
Association between Hernial content and Survival



Chest contents were verified during surgery or by radiographically in cases where infants were not operated due to lack of pre-op stabilisation. Number of organs in the chest cavity were not associated with survival.

Intrathoracic herniation of liver was associated with lesser survival (50% vs 70%, p=0.425) though statistically not significant.

Association between Surgery and Outcome



Throughout the study period policy of pre-op stabilisation was used with almost three-fourth (19 out of 25) of the post operative patients survived to discharge (p=0.003). Surgery was performed on an average 8th day of life (d3-d36) with a mean of 3 days required for pre-op stabilisation, calculated from the time of presentation with respiratory distress in casualty for out born and since birth for inborn.

Primary repair was done in all patients, with post-op complication of wound dehiscence seen in one patient.

Discussion

Due to wide range of anatomic and physiological disturbances found in CDH, responsible for wide variation in clinical state of disease and also due to varied availability of sophisticated health-care technical expertise and treatment protocols, it is very difficult to compare results from various institutes

Survival rate

The study group comprised 30 cases of CDH with an overall survival rate of 63.3% and the survival rate in isolated CDH was 66.7%.

Our study results are comparable to other indian studies by *Anurag Krishna and D. K. Mitra* (1997) who studied 7 children and found that 57% survived and also to a case-series by *Raghvendran et al* (1999) who found an overall survival rate of 62%².

A.N. Gangopadhyay, et al from Institute of Medical Sciences, Banaras Hindu University, Varanasi (2008) had a survival rate of 42.2% from 1996-2006³.

Aruna Jain et al from Lady Harding medical college, new delhi (2002) who found an overall survival rate of 79% for patients presenting from newborn period to late infancy but when age group was restricted only to newborn period the survival rate decreased to 66.7%^{4,56}

While, Shlomo Cohen-Katan et al from Isreal (2009) demonstrated survival rate of symptomatic newborns with CDH of about 37% for the period 1988-2006, with the difference in mortality rates between the group of infants born before 1992 (100% death rate) and those born after 1992 (57% death rate). This kind of difference between epochs can be caused by a change in approach to CDH or more advanced equipment.⁷

Colvin J et al (2006) from western Australia showed a survival rate of 52% of all live-born infants in a comprehensive population based outcome of CDH from the period over (1991- 2002), however our results cannot be compared to this study as this study was a population based study estimating overall incidence and excluding case selection bias such as specific population groups for ex. neonates reaching tertiary care nicu⁸.

However, we found other studies with survival rates higher than ours; *Stanley J, Crankson et al* (2005), demonstrated an overall survival rate of 68%^{9,10}. The most recent outcome data from Columbia University (New York) shows a 75% survival among their last 120 infants, with 13% requiring ECMO support; the survival rates better than ours could be attributed to more advanced health care associated practices in western world such as use of iNO, ECMO and better transport facilities^{11,12,13,14}.

Location of delivery

The survival rate was higher in our Inborn babies with CDH compared to that in Out born, which was due to early management including resuscitation in the delivery room, medical stabilization in the early stages after birth and the use of gentle ventilation to sustain adequate oxygenation while minimizing lung damage before surgery (69% vs 59%, p=0.042). Our results are comparable to the Western Canadian experience with congenital diaphragmatic hernia suggesting 65% survival in inborn¹⁵

As up to one-third of infants with CDH may require ECMO therapy, some authors advocate delivery of infants with CDH in an ECMO centre whenever possible¹⁶.

Prenatal detection

In our study, 40% cases were diagnosed prenatally and prenatal diagnosis was not significantly co-related with improved survival (67% vs 61%, p=0.150), which is in co-relation to most of the studies

suggesting prenatal identification of CDH does not necessarily improve the chance for postnatal survival; however in our study exact timing of antenatal diagnosis in relation to gestational age could not be documented from available data retrieved from medical records department.

There are studies demonstrating a two to four fold increase in mortality among prenatally diagnosed CDH patients when compared with postnatally diagnosed patients⁹¹⁷¹⁸.

According to the recently published study by tertiary Brazilian centre, Perinatal mortality was very high in prenatally diagnosed 38 cases of congenital diaphragmatic hernia. Earlier perinatal deaths are associated with the presence of other structural defects (55%) or chromosomal abnormalities(23%)¹⁹.

It is possible that prenatal diagnosis detects cases with a greater degree or longer duration of visceral herniation and thus an increased severity of pulmonary hypoplasia⁶⁷.

Mode of delivery

LSCS was the preferred mode of delivery (67%), with an overall survival rate better than normal vaginal delivery which was statistically not significant (70% vs 50%, $p = 0.176$), which correlates well with recent studies reporting no significant differences in overall survival between patients born by spontaneous vaginal delivery, induced vaginal delivery and elective caesarean section⁹²²²³.

Birthweight

We found comparatively greater birthweights in survivor group (2862g vs 2717g, non survivors); which is corresponding to studies by Timothy P. Stevens et al (2009) who found that greater birth weight was associated independently with survival²². Low birth weight has been identified as independent risk factors for poor outcomes⁹.

Site of the defect

In present study, right sided hernia was associated with better survival compared to left sided CDH (83% vs 58.3%, $p = 0.440$), which is correlated to the study by *Schaible, Thomas et al* (2004-2009) in which there was a strong trend toward better survival in infants with right-sided CDH than with left CDH (94% vs. 70%; $p = .07$)^{8,18}

But, *Akinkuotu AC et al* (2015) found no difference in duration of tracheal intubation, hospital stay, need for supplemental oxygen at 30-d of life or 6-mo mortality between right and left sided CDH groups, similar to findings by J. E. Wright et al (2010).^{24,925}

While *Fisher JC* (2008) found lesser survival in Right CDH compared with Left CDH (55% vs 77%, $P < .01$)²⁰.

Lung to head ratio

In our study, the measurement of lung area to head circumference ratio (LHR) with the use of 2- dimensional ultrasound was most commonly used method to assess fetal lung volume, and subsequent outcomes, which is also used in most of the studies LHR <1 was significantly correlated with poorer outcome ($p = 0.057$, CI90%)⁹²⁶⁻³²

Age of presentation

Overall survival was lesser for babies with early day presentation compared to late (>24 hrs) presentation (45% vs 80%, $p = 0.328$), which is also shown in recent studies;

Katarina Bojanić et al(2005) showed survival with early presentation was 48% and with late presentation 95 % ($P < 0.001$)³¹

Considering the fact that almost 92% of inborn babies (12 out of 13) were diagnosed antenatally and were admitted to nicu on day one itself irrespective of symptomatic presentation, even excluding them also showed that out of those presenting in outborn earlier presentation (8 out of 17) was associated with lesser survival (38% vs 78%) which is also shown in other Indian studies.

A.N. Gangopadhyay et al found survival rate of 15.5% for those presenting within first 7 days of life and 62% for those neonates presenting after 7 days with an overall survival rate of 42.2%³

However there is much bias between published studies regarding time allotted for the patients to be considered as presenting early, with time frame ranging from <6 hrs to 7 days.

Pulmonary hypertension

Echocardiography by pediatric cardiologist was done within 48 hrs for most of the babies and echocardiography confirmed moderate to severe pulmonary hypertension was present in 33.3% patients and was associated with lesser survival (45% vs 84%, $p = 0.225$), however we were not able to do echocardiography for 3 expired patients in early presentation group because of aggressive refractory respiratory failure.

In addition to the severity of lung hypoplasia, the degree of pulmonary hypertension is equally important. Higher pulmonary artery pressure were associated with decreased survival at all times when compared with normal pressure survivors 60% ($p < 0.003$)³³⁻³⁵

Isolated CDH and CDH with associated anomalies

In our case series, 80% cases were of isolated CDH with a survival rate of 66.7 %, this survival rate is comparable to study by Stanley J, Crankson et al (2005), demonstrated a survival rate of 67% in isolated CDH⁹¹⁰.

The presence of associated malformations increases mortality 4-6 folds. Isolated CDH cases are more likely to survive and have lower morbidity than those occurring as part of a syndrome⁹⁸³⁶³⁷³⁸¹⁸²⁵

Delayed surgery, surgical outcome

The definitive treatment in CDH is surgery. Throughout the study period, a policy of delayed surgery after preoperative stabilization of the infants was practiced³⁹⁻⁴¹. Five patients (16.7%) could not make it through the pre-op stabilisation and expired before they could be taken up surgery. 76% of postoperative infants (19 of 25) survived (including out born); that rate is equal to the result of Clark et al. [101] who studied the surgical characteristics of CDH and found a 75% survival rate among 373 infants who underwent corrective surgery, identical to that in the cohort of Harmath and collaboration and are inferior to Stanley crankson et al(2005), who documented survival rate of 92% in post-op patients¹⁰⁴⁴

In present study the median age of hernia repair was 3 days after admission to nicu, this is comparable to other three contemporary studies in which median age of hernia repair reported was 24 hours to 4 days after admission to intensive care⁷⁸⁴²

Intrathoracic Hernial Contents

In present study, there was no co-relation in regards to number of organs in chest cavity with survival However herniation of liver was associated with poor outcome. The difference in survival rate that we found between infants with the liver present or absent in the thoracic cavity (50% and 30%, respectively) this is comparable to most published studies⁹⁴³³⁰.

Summary

Out of them 43% were Inborn and 57% were Out born referred to BJWHC. Inborn had a comparatively better survival rate than outborn, which was due to early management including resuscitation in the delivery room, medical stabilization in the early stages after birth and the use of "gentle ventilation" to sustain adequate oxygenation while minimizing lung damage before surgery (69% vs 59%, $p = 0.042$).

Prenatal diagnosis was known in 40% patients from the cohort and it did not improve outcome (67% vs 61%, $p = 0.150$).

Over all sex distribution ratio for male : female was 1.7:1, with male to female survival ratio of (57% vs 73%, $p = 0.176$).

Over all Caesarean section rate was 67% with a survival rate marginally better than in normal vaginal delivery and Caesarean section was the preferred mode of delivery in all of the antenatally diagnosed CDH babies (75%), as per the convenience of attending obstetrician (70% vs 50%, $p = 0.176$).

Lung to head ratio (LHR) was almost statistically significant predictor of mortality with a survival "threshold" of 0.95 ($p = 0.057$, CI90%).

The ratio of left to right CDH ratio was 4:1 with a survival rate of (58% vs 83%, $p = 0.440$) Mean birthweight was higher in survivor group 2862g against 2717g as seen in Nonsurvivors ($p = 0.800$).

Similarly, There is a progressive increase in survival from 45% to 80%

as age of presentation increases from less than 24 hrs to later day two onwards presentation (45% vs 80%, $p=0.328$).

Moderate to severe Persistent pulmonary hypertension, confirmed with echocardiography, was present in overall 33% patients and was associated with lesser survival in affected compared to those with normal pulmonary pressures (45.5% vs 83.4%, $P=0.225$).

Conventional ventilation was the preferred mode of ventilation.

Out of all admitted babies 83.3% babies made it through the pre-op stabilisation and 76% of them were discharged to home ($p=0.003$).

Intrathoracic herniation of abdominal contents did not affect survival with liver herniation being the closest of all to affect survival, associated with 50% mortality, though statistically insignificant (50% vs 70%, $p=0.425$).

Isolated CDH without any associated anomalies were 80% and had a better survival compared to CDH with associated anomalies (66.7% vs 50%, $p=0.574$) In post-op complications, one patient required Nissen fundoplication with gastrostomy because of persistent vomiting and weight loss and another patient had wound dehiscence.

The mean period of ventilation was 8 days (range from 3-43days) and average duration of nicu stay being 22 days (9 – 55 days).

Median for start of feeds was day 14 with full feeds achieved by around day 19.

Conclusions

- The overall survival rate in congenital diaphragmatic hernia was comparable to published Indian studies and foreign literature.
- Lung to head ratio was the single antenatal characteristic that helped in predicting outcome.
- Perinatal deaths were associated with lower birth weight, earlier presentation, out born deliveries, presence of persistent pulmonary hypertension.
- The prevalence of chromosomal abnormalities in perinatal death could not be determined from these data.
- In isolated congenital diaphragmatic hernia had a better survival.
- The antenatal diagnosis allowed better counseling of the parents to prepare them for caesarean section and improving the neonatal care.

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