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Original Research Article

Evaluation of long term outcome of congenital diaphragmatic hernia survivors: a single centre 8 years' experience in a developing nation with limited facilities

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ABSTRACT

Background: The objective of the study was to find out incidence of long term complications in congenital diaphragmatic hernia (CDH) survivors in a developing nation with limited facilities.
Methods: A retrospective study was done on patients who underwent CDH repair at our institution from 2012 to 2019. 71 patients were identified of these 55 patients operated in neonatal age were considered. After applying exclusion criteria 42 patients included in the study were then divided in 2 groups. Group 1 (26 patients): neonates requiring ventilation within 6 hrs of birth and group 2 (16 patients): not requiring ventilation or intubated after 6hrs of birth. Data from medical records were supplemented by a questionnaire regarding perceived physical function and medical follow up till date. Respiratory, central nervous, musculoskeletal and gastrointestinal systems were concentrated upon and questionnaire set. These were then compared with respect to their long term outcomes. Also, overall incidence of these in the two groups combined was noted compared with other studies.
Results: On comparing these 2 groups incidence of long term complications was found more in group 1; however on statistical analysis difference was not significant. As also incidence of individual long term complications in all patients together were identical or lower than in other published series. Mortality in our study was 8 of 49 neonates which was 17% of all patients presenting with CDH or born at our centre.
Conclusions: Despite the growing population of CDH survivors the morbidity is not very significant and most patients lead a normal average active life.

Keywords: Long term complications, Congenital diaphragmatic hernia, CDH sequelae

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a life-threatening congenital anomaly, with an incidence of approximately 1:2,500 live births. As per literature despite advances in antenatal diagnosis and postnatal management, mortality rate remains stable around 40-50%.[1] It has been shown that overall survival rate is mainly determined by the incidence of CDH associated anomalies, degree of pulmonary hypoplasia and pulmonary hypertension in the neonatal period.[2,3] Children born with CDH who survive often suffer from morbidities related to pulmonary hypoplasia and associated anomalies, but also from the sequelae resulting from the intensive care they were exposed to.[2,3] This is one of the reason parents opt for antenatal termination of babies with CDH, whether that is required is questionable. Despite this we, observed that patients following up in our department with these complaints after CDH repair appeared to be very few. So, we decided to conduct this study to find out incidence of long term squeal in CDH survivors and their perceived health; also

to evaluate factors affecting the same, at our institute. This is a retrospective analysis of operated cases of CDH in neonates with a prospective follow up. Survival and long term outcome in these patients is mainly related to lung hypoplasia. So, we decided to compare patients through two groups; patients ventilated within 6 hrs of birth (likely to be having lung hypoplasia more than) the group 2 of our study. This is a cross-sectional study, which enabled us to collect all the data at one time and thereby not lose any patients in extensive follow-ups.

METHODS

From March 2012 to June 2019, 77 patients got admitted with or were born with CDH at our institute (G.G.M.C. and Sir J.J. Hospital). Of these 71 patients were operated for it and amongst remaining 6 patients, 3 patients succumbed prior to surgery due to severe pulmonary hypertension (PH) and associated cardiac anomaly and 3 patients parents refused surgery. Out of these 71 patients only 55 patients were neonates. Further patients who could not be contacted (5 patients) or refused to participate (4 patients) or mortality in early postoperative period (4 patients) were excluded. Remaining 42 patients included in study were then divided in two groups; group 1 (26 patients): neonates requiring ventilation within 6 hrs of birth and group 2 (16 patients): not requiring ventilation (9 patients) or intubated after 6 hrs of birth (7 patients). A retrospective study was done on these patients and they were followed up for long term evaluation. This study was approved by the ethical committee at our hospital and written informed consent was obtained upon inclusion in the study from parents of children.

Data from medical records were supplemented by a questionnaire consisting of questions regarding perceived physical function and medical follow up till date. Only patients with minimum 8 months of follow up were included. Respiratory, central nervous system, musculoskeletal system, hearing and gastrointestinal systems were concentrated upon and questionnaire set. This study is based on study specific questionnaire and interpreted with caution. Multiple scales used, make it more reliable, also because questions were framed both negatively and positively.

These were then compared with respect to their long term outcome. Also, overall incidence of these in the two groups combined was noted and compared with other published identical studies. Along with this; parents of all patients and children above 4 years were enquired about satisfaction about their children and selves compared to other children in society and noted.

After data collection, data entry was done in Excel. Data analysis is done with the help of SPSS Software version 15, association among various study parameters is assessed by Chi-Square test (Fisher Exact test for 2*2 tables). P value less than 0.05 is taken a significant level. As mentioned, a chi-square test was used to test differences among the groups and, for numerical variables; Fischer's exact test was used to make pairwise comparisons between groups.

RESULTS

Of the 42 patients included in the study, 27 were boys and 15 were girls. 12 patients had right sided CDH and 30 were left sided. Only 3 patients were preterm. 7 patients had associated anomalies (16.7%); 6 had cardiac anomaly of which 2 were required to be operated at later age and 1 patient had cleft palate with ARM. 17 patients underwent open repair while remaining 25 were managed by video-assisted thoracoscopic surgery (VATS). Intraoperatively 6 patients had large defects. 2 of these patients underwent primary repair and in 4 patients a mesh was used. Stomach was found herniated in 3 patients in left sided CDH, and liver had herniated in 1 patient. Early postoperative complications were found in 9 patients (sepsis in 1 patient, bronchopneumonia in 1, recurrence in 2 patients which was later re-repaired, wound infection in 1 patient and persistent pulmonary hypertension in 4 patients which required prolonged ventilator support for 14 to 23 days and admission for more than a month in hospital (Figure 1 and Table 1). Long term complications in these patients were assessed on basis of patient and their parents' questionnaire. Mean follow up in group 1 was 3.7 years and in group 2 was 5.8 years. Incidence in both groups combined of respiratory symptoms was found in 2.3%, gastro-oesophageal reflux (GER) is 12%, neurodevelopmental and seizure 4.7%, hearing disability in 2% and musculoskeletal in 12% in the 42 patients in the study.

Table 1: Parameters to compare groups.

Parameter for comparison	Group 1	Group 2
Male:female	18:8	11:5
Left:right	19: 7	12:5
VATS:open	13:13	12:5
Anomalies	5	2
Defect size	Large: 2 Mesh: 1	Large: 5 Mesh: 3
Post-operative complications	5	4
Stomach or liver up	Stomach: 1 Liver: 1	Stomach: 2

The distribution of patients in either group was noted in Table 2. The differences of complications in both groups was given in in Figure 2 and most of the complications occurred in group 1 patient. However, when these differences were tested statistically the difference between the group 1 and 2 was not found to be significant. The two groups individually and combined were then compared from similar published studies. We found that incidence of respiratory complaints,

neurodevelopmental disorders, and hearing disabilities was significantly lower than most other studies. As we have used technique of gentle ventilation with permissive hypercapnia and sildenafil for pulmonary hypertension as also non availability of extracorporeal membrane oxygenation (ECMO) could have been a cause for this. Incidence of GER and musculoskeletal disorders were identical with few studies.

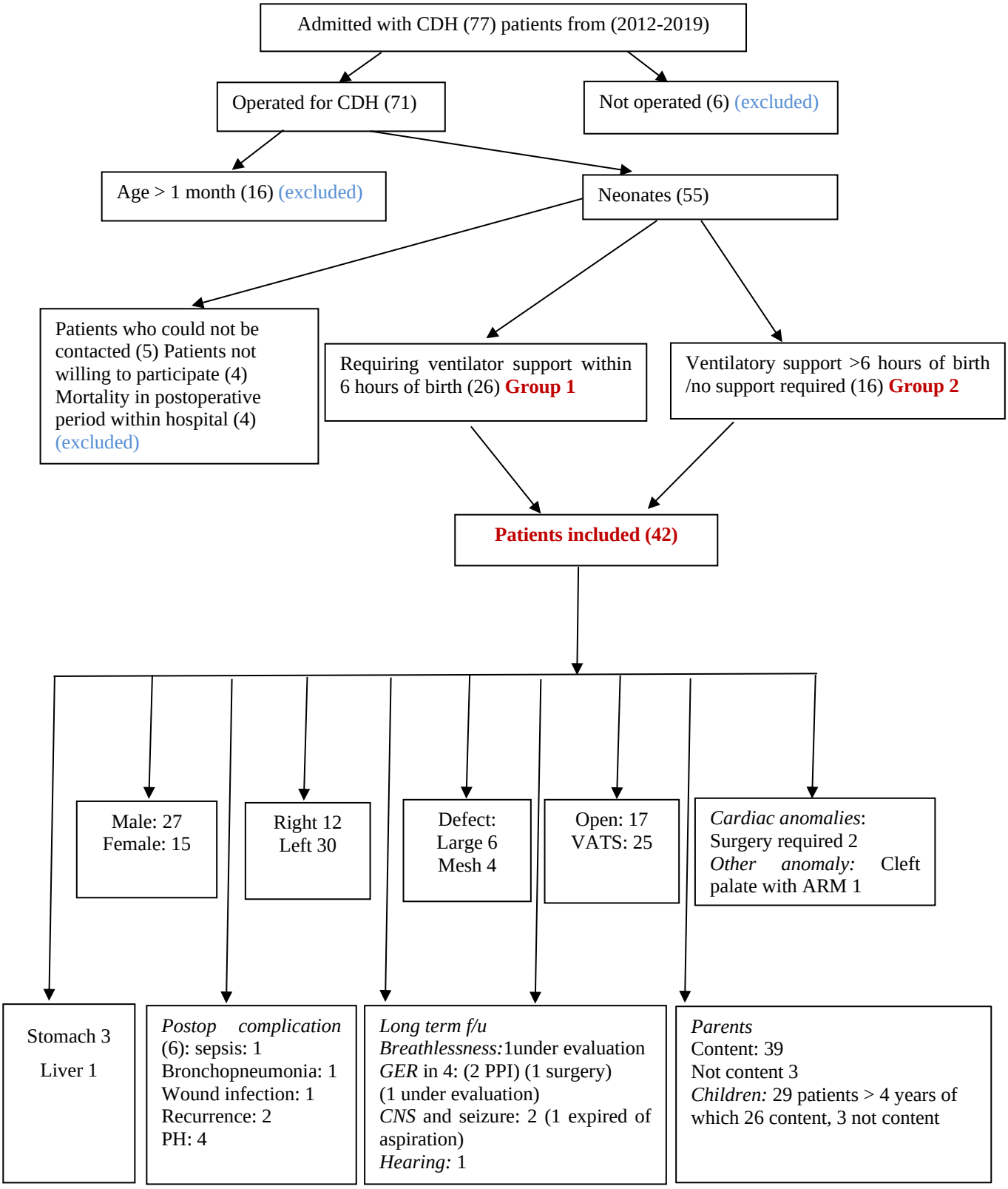

Figure 1: Demographics and results.

Table 2: Comparisons of long term complications.

Parameters compared	Group 1 (n=26) (%)	Group 2 (n=16) (%)	Combined (n=42) (%)
Respiratory complaints and pulmonary hypertension	1 (3.8)	0 (0)	1 (2.3)
GI symptoms and GERD	3 (11.5)	2 (12.5)	5 (12)
Neurodevelopmental abnormality and seizure	2 (8)	0 (0)	2 (4.7)
Hearing abnormalities	1 (3.8)	0 (0)	1 (2.3)
Musculoskeletal abnormalities and scoliosis	2 (7.7)	3 (18.8)	5 (12)
Weight for age	50-75 normal percentiles. Except 1 patient with suspected GER 25-50 percentiles	50-75 percentile normal	
Parents content			38 (92)
Patient content >4 years age			37 (90)

Table 3: Association among study groups for respiratory system.

Breathlessness		Study group		Total
		Group 1	Group 2	
Yes	No.	1	0	1
	%	3.8	0.0	2.4
No	No.	25	16	41
	%	96.2	100.0	97.6
Total	No.	26	16	42
	%	100.0	100.0	100.0
Chi-square tests	**Value**	**df**	**P value**	**Association is**
Pearson Chi-square	0.630	1	0.427	Not sig
Fisher's exact test			1.000	

Table 4: Association among study groups for GER.

GER		Study group		Total
		Group 1	Group 2	
Yes	No	3	2	5
	%	11.5	12.5	11.9
No	No	23	14	37
	%	88.5	87.5	88.1
Total	No	26	16	42
	%	100.0	100.0	100.0
Chi-square test	**Value**	**df**	**P value**	**Association is**
Pearson Chi-square	0.009	1	0.926	Not sig
Fisher's exact test			1.000	Not sig

Table 5: Association among study groups for neurodevelopmetal disorders.

Neurodevelopmental & seizure		Study group		Total
		Group 1	Group 2	
Yes	No.	2	0	2
	%	7.7	0.0	4.8
No	No.	24	16	40
	%	92.3	100.0	95.2
Total	No.	26	16	42
	%	100.0	100.0	100.0
Chi-square tests	**Value**	**df**	**P value**	**Association is**
Pearson Chi-square	0.152	1	0.696	Not sig
Fisher's exact test			0.754	Not sig

Table 6: Association among study groups for hearing.

Hearing		Study group		Total
		Group 1	Group 2	
Abnormal	No.	1	0	1
	%	3.8	0.0	2.4
Normal	No.	25	16	41
	%	96.2	100.0	97.6
Total	No.	26	16	42
	%	100.0	100.0	100.0
Chi-square tests	**Value**	**Df**	**P value**	**Association is**
Pearson Chi-square	0.630	1	0.427	Not sig
Fisher's exact test			1.000	Not sig

Table 7: Association among study groups for musculoskeletal deformity.

Deformity		Study group		Total
		Group 1	Group 2	
Yes	No	2	3	5
	%	7.7	18.8	11.9
No	No	24	13	37
	%	92.3	81.3	88.1
Total	No	26	16	42
	%	100.0	100.0	100.0
Chi-square test	**Value**	**df**	**P value**	**Association is**
Pearson Chi-square	1.155	1	0.283	Not sig
Fisher's exact test			0.352	Not sig

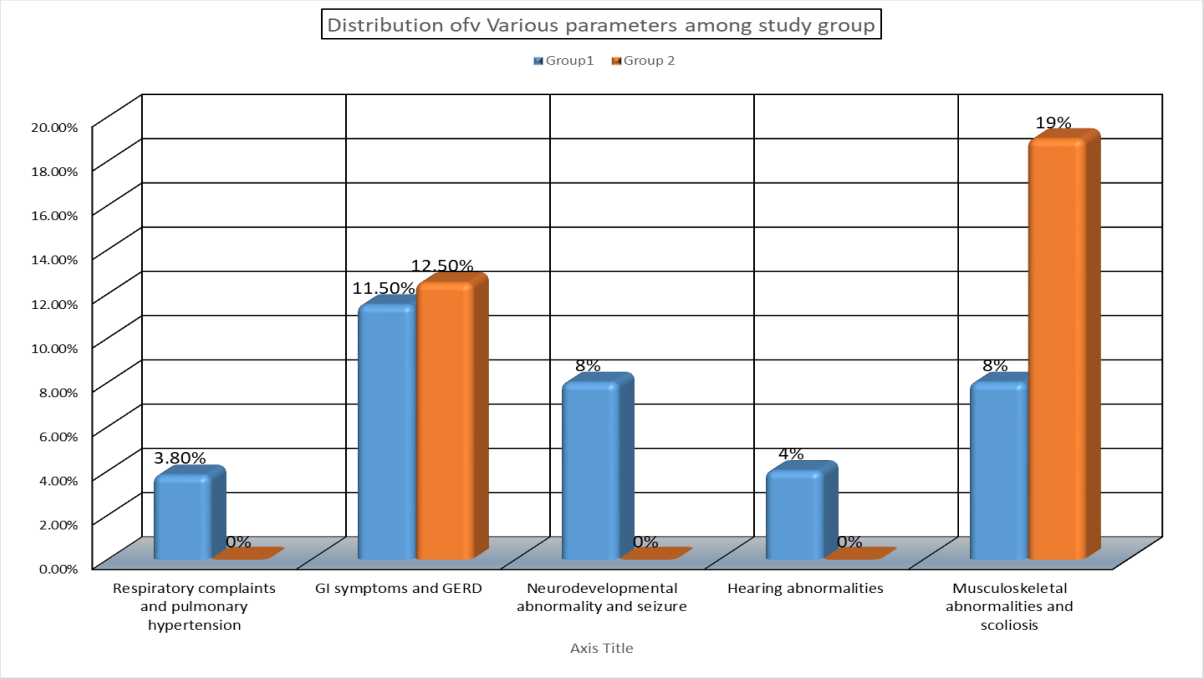

Figure 2: Distribution of various parameters among study group.

DISCUSSION

CDH is a severe congenital anomaly with its mortality reported; ranges from 40% to 50% to as low as 10% in various papers in English literature.[1] In our study we found it to be 17%. This is mainly decided by the degree of lung hypoplasia, PH and severity of associated anomalies. Also, in developing nations like ours, another

added factor is non availability of ECMO and at times high frequency oscillatory ventilation. At our centre inborn CDH patients or referred cases, when required are ventilated conventionally on synchronized intermittent mandatory ventilation mode, gentle ventilation with permissive hypercapnia. If there is severe or worsening respiratory acidosis they are started on sildenafil; initially infusion from day 1 in dose of 2 mg/kg/day. 2DECHO (2D echocardiography) is done at earliest and if there is no PH sildenafil is stopped over 5 days or in case of PH it is continued till 2D echo shows improvement or no PH and tapered over a week after this. When possible it is then shifted to oral dosage. Due to non-availability of ECMO and non-affordability of these patients some patients have found to worsen and succumb. As in our study 3 patients prior to surgery and 4 after surgeries expired probably due to same. This contributed to 12% of all CDH neonatal patients admitted at our institute. In other papers we found mortality as 15% despite ECMO and 45-50% of patients who received ECMO could not be saved.[2,3]

The new born CDH patients who managed to breathe spontaneously for at least first six hours (group 2) were assumed to be the least affected by the pulmonary hypoplasia, compared to the patients who required ventilator support at birth or within 6 hrs (group 1).[2] However when these groups were compared with respect to individual long term effect the differences were found to be statistically non-significant.

Both groups combined were then assessed and compared with other studies. As is evident from the study respiratory complications as assessed by breathlessness and limited activity is present in only 1 patient of 42 included in study (2.3%). As compared to study by Icono et al 17% and Shwartz et al 38%.[4,5] As per study Ost et al it is 46% in identical groups.[2,3] Symptoms of and diagnosis of GER and other gastrointestinal complications in our study was 12% which is identical with study by Ost et al in comparative set of patients. However, it is documented high as 60% by Vanamo et al and as 20-23% by Koot et al and Fasching et al.[6-8] Comprehensive measurements of gastroesophageal reflux are probably necessary to obtain a more accurate picture.

Neurodevelopmental morbidity was found in 2 babies who are in special school also hearing defect was found in one of these babies who also had seizure disorder on medications. This child had developed convulsion and expired due to aspiration pneumonitis and subsequent sepsis at age 1.5 years. Thus, incidence of neurodevelopmental disorder was 4.7% as compared to 46% in comparative groups. Treatment of newborns with persistent pulmonary hypertension used to consist of hyperventilatory induced alkalosis. These infants were exposed to significantly higher pH values for longer periods and needed longer durations of mechanical ventilation resulting in approximately 35% of children requiring hearing aids.[9-11] We followed the principle of gentle ventilation and permissive hypercapnia. Hearing disability was found in 2% children in this study as compared to 6% reported by Danzer and 27% by Lund et al.[12,13] Morini et al reported that 49% (40) of the 82 CDH survivors (non-ECMO) had sensorineural hearing loss at audiologic follow-up at a median age of 3.0 years.[14]

Incidence of musculoskeletal defects was found in 12% which is identical with study by Lund et al.[12] However, it is 23-27% as reported by Ost et al and Vanamo et al.[2,8] 3 out of 5 patients having in drawing of chest or scoliosis on retrospective analysis had large defects but sutured primarily without mesh. However, 4 other patients with large defects where mesh was used did not have any such abnormality.

Weight for age was found within normal range for all patients except one who has symptoms suggestive of GER and is being evaluated. One patient who has undergone fundoplication and 2 other patients treated for GER with no residual symptoms now have weight for age within normal limits. No other patients have any eating complaints.

As for patient and parent satisfaction and quality of life assessment score no specific scoring system was followed hence the results cannot be compared with other series. However single question answers were obtained as yes or no; to their satisfaction with the child compared to other healthy children in their community and school and similarly from patients themselves for the ones above 4 years age whether they were content or felt deficient compared to other normal children around. 92% parents were content and 90% patients themselves were content. However, a standardised scoring system needs to be used to evaluate quality of life index.

As more of CDH patients are now surviving there is a fear for long term morbidity and decreased quality of life in these children and their parents.[1-3] But what needs to be mentioned is that patients with severe PH and anomalies constitute only a subset of all CDH patients. As in our study, patients with severe PH and associated severe anomalies were 12% who could not survive and could have had severe long term complications and disabilities. But major subset 88% as is evident from study show lower incidence of long term morbidity as compared to other studies.

More number of parents today opts for termination of babies with CDH and dreads the long term complications and quality of life. It is hence important to re-review these long term complications and mortality for our CDH patients and survivors and document same along with patient and parental satisfaction and its true picture.

Despite limited facilities we found mortality rate and long term complications in CDH survivors to be lower than a few studies compared and identical in some respects with others. Although ECMO is required to save some of our

patients with severe PH it has also caused some of the long term complications. Yet a large number of CDH survivors are still without these complications and limitations.

CONCLUSION

Despite the growing population of CDH survivors the morbidity is not very significant and most patients lead a normal average active life. However alternative solution and pharmacological treatments need constant trial to lessen morbidity and increase survival. It is highly recommended that children born with CDH are evaluated periodically in a protocolized multidisciplinary setting to minimize short-term morbidity and to assess long-term morbidity document the same.

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Ethical approval: The study was approved by the Institutional Ethics Committee of G.G.M.C. and Sir J.J. Hospital

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