

Is there a determining factor that predicts mortality in patients with congenital diaphragmatic hernia?

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Abstract

Aim: This study was designed to investigate the factors affecting the prognosis in neonates with congenital diaphragmatic hernia (CDH) who were treated in our clinic. These factors included prenatal lung-head ratio (LHR), prenatal stomach and liver presence in the thorax, blood gases in the first 24 h and the modified ventilation index (MVI).

Material and methods: The study was carried out retrospectively in 30 neonates with prenatally diagnosed left CDH who were treated in our clinic between January 2007 and 2013. Data were collected, evaluated, and statistically analyzed for gender, birth weight, gestational age, prenatal LHR, prenatal presence of stomach and liver in the thorax, postnatal initial blood gases in the first 24 h and MVI.

Results: The median LHR for non-survivors was 1.49 and for survivors 1.51. No statistically significant difference in LHR was detected between survivors and non-survivors. In 19 neonates, prenatal ultrasonography (USG) revealed intrathoracic stomach, and 9 of these infants died. Intrathoracic liver was seen in 15 neonates, and 9 of these died. A statistically significant difference was not found between survivors and non-survivors in the intrathoracic liver or intrathoracic stomach neonates. A comparison between the non-survivors and survivors showed a median pH value of 7.10 in non-survivors and 7.24 in survivors ($p = 0.002$). The median PaCO₂ value was 69.4 mm Hg in non-survivors and 51.9 mm Hg in survivors ($p = 0.01$). There were statistically significant differences in pH and PaCO₂ values. The median value of MVI was 33 in survivors and 100 in non-survivors. There was a statistically significant difference between overall non-survivors and survivors in the MVI value ($p < 0.05$).

Conclusions: Based on the findings, postnatal pH, and PaCO₂ and MVI values are favorable prognostic factors in CDH in our selected group of patients.

Key words: congenital diaphragmatic hernia, prenatal diagnosis, prognostic factors.

Streszczenie

Cel: Badanie przeprowadzono, aby ocenić czynniki wpływające na rokowanie u noworodków z wrodzoną przepukliną przeponową (CDH) leczonych w klinice autorów. Czynniki te obejmowały prenatalny współczynnik płuco-głowa (LHR), obecność żołądka i wątroby w klatce piersiowej, gazometrię krwi w pierwszych 24 godzinach oraz zmodyfikowany indeks wentylacji (MVI).

Materiał i metody: Do badania włączono retrospektywnie grupę 30 noworodków, u których prenatalnie stwierdzono lewostronną CDH, leczonych w klinice autorów pomiędzy styczniem 2007 a 2013 r. Zebrano, oceniono i poddano analizie statystycznej dane dotyczące płci, masy urodzeniowej, wieku ciążowego, przedurodzeniowej wartości LHR, przedurodzeniowej obecności żołądka i wątroby w klatce piersiowej, wyników pourodzeniowej gazometrii w pierwszych 24 godzinach oraz wartości MVI.

Wyniki: Średnia wartość LHR u noworodków, które nie przeżyły, wyniosła 1,49, a u ocalałych 1,51. Nie stwierdzono statystycznie znamiennej różnicy w zakresie wartości LHR pomiędzy tymi grupami. W prenatalnym badaniu ultrasonograficznym wykryto obecność żołądka w klatce piersiowej u 19 noworodków – 9 z nich zmarło. Obecność wątroby zaobserwowano u 15 noworodków – 9 zmarło. Nie wykazano statystycznie znamiennej różnicy pomiędzy noworodkami ocalałymi i zmarłymi w zakresie obecności wątroby lub żołądka w klatce piersiowej. Porównanie pacjentów zmarłych z ocalałymi wykazało medianę wartości pH na poziomie 7,10 w grupie zmarłych i 7,24 w grupie ocalałych ($p = 0,002$). Mediana wartości PaCO₂ wyniosła 69,4 mm Hg w grupie zmarłych i 51,9 mm Hg w grupie ocalałych ($p = 0,01$). Różnice pomiędzy wartościami pH i PaCO₂ były znamienne statystycznie. Również znamienna statystycznie ($p < 0,05$) była różnica pomiędzy średnią wartością MVI u noworodków ocalałych (MVI = 33) a wartością tego parametru u noworodków zmarłych (MVI = 100).

Wnioski: Na podstawie wyników można stwierdzić, że pourodzeniowe wartości pH, PaCO₂ i MVI stanowią użyteczne czynniki rokownicze w omawianej grupie pacjentów.

Słowa kluczowe: wrodzona przepuklina przeponowa, rozpoznanie prenatalne, czynniki rokownicze.

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Introduction

Congenital diaphragmatic hernia (CDH) is a rare congenital anomaly causing severe respiratory distress. In this abnormality, the abdominal organs enter the thorax through a diaphragmatic defect. Although it varies between 1/2000 and 1/5000, its incidence is believed to be higher due to stillbirths and terminations of pregnancy due to accompanying lethal anomalies. Factors such as pulmonary hypoplasia and pulmonary hypertension lead to high mortality and morbidity rates in babies born with this condition [1–3]. Hence, many factors have been proposed to explain the prognosis of the high mortality, including lung-heart ratio (LHR), presence of stomach or liver in the thorax, blood gases in the first 24 h and the modified ventilation index (MVI). Because of the limited number of cases, no single factor alone has been proven to determine the prognosis.

Aim

In this study, we aimed to evaluate whether factors such as prenatal LHR, presence of stomach or liver in the thorax, blood gases in the first 24 h and MVI in infants who were treated in our clinic contributed to the prognosis in prenatally diagnosed CDH.

Material and methods

This study was carried out retrospectively in the Istanbul Faculty of Medicine, Department of Pediatric Surgery with 30 isolated CDH patients seen between January 2007 and December 2013. All the neonates were diagnosed and followed up in the Division of Perinatology of the University prenatally and transferred to the Department of Pediatric Surgery. All of the lesions were left sided. The associated anomalies were bilateral grade II hydronephrosis in 1 patient, cleft palate in 1 patient, patent ductus arteriosus (PDA) in 1 patient, atrial septal defect (ASD) in 2 patients, patent foramen ovale (PFO) in 1 patient, and PDA and ventricular septal defect (VSD) in 1 patient.

All of the patients underwent prenatal two-dimensional ultrasonography and had a prenatal diagnosis of CDH. The LHR was measured prenatally by two-dimensional ultrasonography; the two longest perpendicular diameters of the contralateral lung are multiplied and this is divided by head circumference (in mm) [4]. All diagnoses were made prenatally at 24–26 weeks of gestational age and LHR was measured at the same time. The deliveries were all sectio. The prematurity rate was 5/30 (16.7%).

The time of the surgery was 2.5 ± 1.1 days. We did not use a patch in any of the cases.

Twenty-one newborns had normal chromosomal analysis, 8 patients refused analysis, and 1 patient had t(1,5) (p21;p14) on analysis. The mean time of newborns stay at the hospital was 22.2 ± 18.8 days. We do not have extracorporeal membrane oxygenation (ECMO). The presence of the stomach or liver in the thoracic region was also noted during ultrasonography. Upon delivery, the newborns were transferred to our neonatal intensive care unit (NICU). Con-

ventional ventilation was used in all cases. Following hemodynamic and respiratory stabilization ($\text{pH} > 7.45$, $\text{PaCO}_2 < 60$ mm Hg, and $\text{PaO}_2 > 45$ mm Hg), the patients underwent the operation. Each prenatally diagnosed neonate's sex, gestational weight, gestational age, LHR, presence of stomach or liver in thorax, blood gases in the first 24 h and MVI were recorded. The MVI is a parameter defined in determining the prognosis of neonates with CDH under mechanical ventilation [5]. It is calculated from the factors of PIP, ventilatory frequency, and PCO_2 ($\text{PIP} \times \text{PCO}_2 \times \text{ventilation frequency}/1000$).

Statistical analysis

Descriptive statistical methods were used to analyze the results for the groups. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for the normality analysis. ANOVA and *t*-test methods were used to compare the groups and to ensure that a normal distribution was found. The Kruskal-Wallis test was used for the variance analysis, and the Mann-Whitney *U* test was used to compare the groups that did not have a normal distribution. Ninety-five percent was accepted as the confidence interval, and a *p*-value ≤ 0.05 was considered significant for the analysis.

Results

Of the 30 neonates enrolled in the study, 20 (66.6%) were male and 10 (33.3%) were female, mean gestational weight was 2900 ± 471 g, and mean gestational age was 37.8 ± 1.6 weeks.

Data were grouped and analyzed according to mortality. Overall mortality was 14 (46.6%). Fourteen of the 30 neonates died. Eleven (55%) of them were male and 3 (33%) were female. Seven neonates died before surgery and 23 neonates underwent operations. The mean defect area in our patients was 3×4 cm and no patch was used in any of our patients. Of these 23 patients, 7 died post-operatively.

Among 13 patients with $\text{LHR} < 1.4$, 7 (53%) neonates were lost. Among 17 neonates whose LHR was > 1.4 , again 7 (29%) neonates were lost. The median LHR in the overall group was 1.6. (For non-survivors it was 1.49 and for survivors 1.51.) No statistical significance was detected among the groups according to LHR .

The stomachs were present in the thoraxes of 19 (63.3%) patients, 9 (47%) of whom died. The livers were present in the thoraxes of 15 (50%) neonates, and 9 (60%) of them died. A statistically significant difference was not found between survivors and non-survivors in the intrathoracic liver or intrathoracic stomach groups either (Tab. I).

For the evaluation of the prognostic values of LHR , pH , PaCO_2 , PaO_2 , base excess in the extracellular fluid compartment (BE_{ecf}), and cHCO_3 , the neonates were grouped as total non-survivors and survivors. From perinatal delivery until discharge, 14 neonates were lost and 16 neonates survived. A comparison between the non-survivors and survivors showed a median pH value of 7.10 in non-survivors and 7.24 in survivors ($p = 0.002$). The median PaCO_2 value was 69.4 mm Hg in non-survivors and 51.9 mm Hg in sur-

Tab. I. Distribution of demographic data according to mortality ($n = 30$)

Parameter	Male ($n = 20$)	Female ($n = 10$)	LHR < 1.4 ($n = 13$)	LHR > 1.4 ($n = 17$)	Stomach in thorax ($n = 19$)	Liver in thorax ($n = 15$)
Total	11/20	3/10	7/13	7/17	9/19	9/15
Exitus	(55%)	(33%)	(53%)	(41%)	(47%)	(60%)

vivors ($p = 0.01$). There were statistically significant differences in pH and PaCO₂ values (Tab. II).

For investigating the prognostic value of MVI, the data were compared between overall non-survivors and survivors. The median MVI value in non-survivors was 100 (32–167), whereas in survivors it was 33 (19–63). Only 1 neonate was lost with MVI < 37; however, all the neonates were lost with MVI > 80. There was a statistically significant difference between overall non-survivors and survivors in the MVI value ($p < 0.05$).

To determine a threshold value for MVI, an receiver operating characteristic (ROC) curve was generated. The MVI threshold value was 37 with a sensitivity of 92% and specificity of 82% (Fig. 1).

Discussion

The search for prognostic factors affecting the CDH prognosis has been a long process. It may be that a sole factor will not be singled out to determine the survival for this congenital anomaly, but rather, a combination of several factors will have to be taken into account [6].

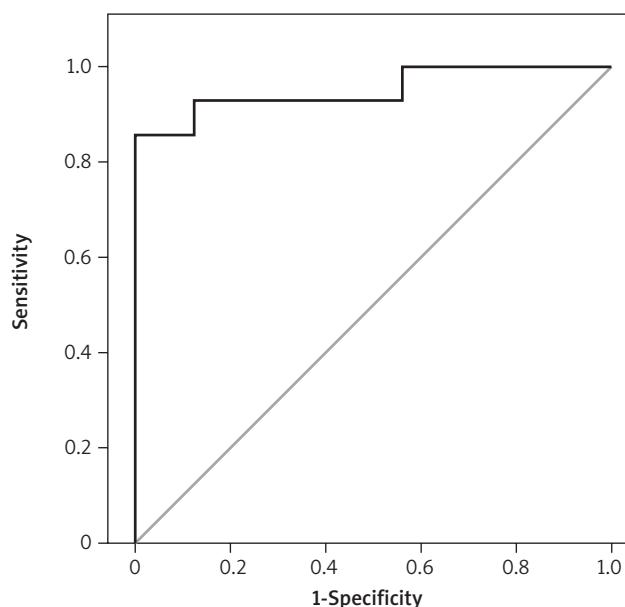
The LHR calculated by prenatal ultrasound was first described by Metkus *et al.* in 1996. Fifty-five neonates were reviewed in this retrospective study, and it was reported that all neonates were lost when LHR was < 0.6, and 61% of neonates survived when LHR was 0.6–1.30. Survival reached 100% when LHR was > 1.4 with the aid of ECMO and conventional therapies [7]. Following this report and many others, mortality and morbidity were shown to decline when LHR was < 1.0 [8]. Based on this information, experimental studies with fetal tracheal occlusion are continuing in North America and Europe [9]. However, because there are a limited number of cases and every clinic has unique criteria for selecting patients, standardized protocols for LHR have not been established. In our study, no statistically significant difference in LHR was observed between survivors and non-survivors. However, 4 out of 6 of our patients with LHR below 1.0 were lost. This provides a clue about this parameter, which should be investigated within a larger study population.

The presence of the stomach in the thorax is another prognostic factor that has been proposed in survival. Burge *et al.* reported high mortality in their study investigating the prognostic effect of stomach position; that is, when the stomach was in the thorax, mortality was greater, but when the stomach was in the abdomen, survival was 100% [10]. Hatch *et al.* reported survival of 93% when the stomach was below the diaphragm and 29% when it was in the thorax [11]. In a multicenter study from Japan, Usui *et al.* defined intrathoracic stomach as when more than

Tab. II. Comparison between survivors and non-survivors

Parameter	Non-survivors ($n = 14$) Median	Survivors ($n = 16$) Median	P -value
LHR	1.49	1.51	0.498
pH	7.10	7.24	0.002*
PaCO ₂	69.4	51.9	0.01*
PaO ₂	40.9	51.3	0.064
BEecf	-7.5	-4.8	0.101
cHCO ₃	14.3	18.3	0.131

Mann-Whitney U Test. * $P < 0.05$.

**Fig. 1.** Receiver operating characteristic curve for modified ventilation index (AUC = 0.95; $p = 0.042$)

half of the stomach was herniated into the thorax. Of the 117 neonates enrolled in their study, the stomach was found in the thoraxes of 70% of the neonates in the high-risk group, 25.7% in the medium-risk group, and 4.2% of neonates in the low-risk group. Survival was reported at 20% in the high-risk group, 74.3% in the medium-risk group, and 100% in the low-risk group [12]. In our study, the stomach was present in the thoraxes of 63.3% of the neonates, and survival was 53%, which is lower than in the previous series. Nine neonates were lost in the intrathoracic stomach group and five neonates were lost in the intra-abdominal stomach group. The presence of the stomach in the thorax did not relate to survival in our study. This result is not concordant with the literature, which was attributed to pulmonary hypertension.

The presence of the liver in the thorax is a factor for determining prognosis and planning fetal interventions. In the antenatal CDH registry group, Jani *et al.* reported 86 intra thoracic livers out of 184 neonates [13]. In the same study, previous reports were also evaluated. The study of Metkus *et al.* included 38 neonates of which 80% had intrathoracic livers, while Heling *et al.* reported a rate of 64% for intrathoracic livers in 22 neonates. Victoria *et al.* conducted a study with 85 neonates, wherein 51 (60%) had intrathoracic livers and 23 were lost with a 45% survival rate [14]. In their meta-analysis, Mullasery *et al.* evaluated 21 studies that were published in the Medline and Embase databases. These studies focused on the presence of the liver in thorax. There were 407 livers detected in thoraxes. Of the 407 neonates, 222 were lost and 185 survived; overall survival was 45.4% [15]. In our study, 9 of 15 neonates with intrathoracic livers were lost and 5 of 15 neonates with intra-abdominal livers were lost; survival was 40% for these patients. A statistically significant difference between the groups was not revealed; therefore, the presence of the liver in the thorax could not be shown as a prognostic factor, contradicting the current literature. Pulmonary hypertension was the main reason for this discrepancy.

Blood gases in the first 24 h have been proposed as a prognostic factor in many studies since Boix-Ochoa presented their report in 1974 [16]. Early era studies showed an association with pH, PaCO₂, and mortality between survivors and non-survivors. Low PaCO₂ and high PaO₂ levels that were either previously normal or corrected by mechanical ventilation have been found to be related to a good prognosis. On the other hand, despite mechanical ventilation, persistently high levels of PaCO₂ were related to a poor prognosis. Blood gases have also been investigated for timing of surgery when pre-operative preparations were deemed necessary. Gentili *et al.* reported that pH > 7.35 with PaCO₂ < 55 mm Hg is a valid indicator for pre-surgical stabilization and surgical intervention [17]. Haricharan *et al.* stated that hypercapnia in initial blood gases is related to high mortality [18]. Similarly, Hoffman *et al.* reported a survival rate of 27% when PaCO₂ < 60 mm Hg, but all the patients were lost when PaCO₂ > 70 mm Hg [19]. Neonates who were lost in our study had median pH at 7.1 and median PaCO₂ at 69.4 mm Hg, whereas survivors had median pH at 7.24 and median PaCO₂ at 51.9 mm Hg. Low pH and high PaCO₂ levels between survivors and non-survivors had statistical significance, consistent with previous reports.

The MVI is a parameter that relates PaCO₂ to peak inspiratory pressure in mechanically ventilated patients. Norden *et al.* reported their results of a study associating pre-operative PaCO₂ values and ventilatory indices obtained in the first 24 h in 90 neonates. They showed that the MVI threshold value must be 40 for survival [20]. When the MVI is < 40, they predicted the survival rate at 91% with a sensitivity of 94% and specificity of 85%. Dimitriou *et al.* studied the blood gases and MVI values by calculating the lung area to determine the prognosis and MVI threshold. They observed an average of 49 in the good prognosis group [21]. Ilce and

Celayir revealed similar values in their study with 30 CDH patients. Of the 30 patients, the mean MVI value of the survivors was 38.8, but the non-survivors' mean MVI value was 114.3 [5]. In our study, median MVI value for survivors was 33 and for the non-survivors was 100. We found a threshold value of 37 for MVI for predicting mortality. The MVI values were < 40 in 92% of our neonates, which were all lost. All neonates with MVI > 80, as suggested by previous reports, were lost.

This study has limitations due to its retrospective nature and limited number of cases. The limited number of patients did not permit two analyses missing for a prediction study, i.e. a multivariate analysis and analysis of AUC/predictive value. Another limitation of the study is that the protocol of these patients is unique for our study; this prediction model pertains to this center and neonatal protocol, so it may not be applicable elsewhere. However, one advantage of our study is that there are no missing values in any of the patients. The mentioned parameters are evaluated in all of the patients.

Conclusions

In light of these findings, pH, PaCO₂ levels and MVI have a positive predictive value in prognosis. LHR, liver, and/or stomach presence in the thorax could not be related to prognosis. Future research is necessary to reveal the outcome of the prognostic factors in isolated CDH as well as long-term morbidity.

Disclosure

Authors report no conflict of interest.

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