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ORIGINAL ARTICLE

Best pre-ductal PaO_2 prior to extracorporeal membrane oxygenation as predictor of mortality in patients with congenital diaphragmatic hernia: a retrospective analysis of a Japanese database

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Abstract

Purpose Predicting lethal pulmonary hypoplasia in infants with congenital diaphragmatic hernia (CDH) before extracorporeal membrane oxygenation (ECMO) initiation is difficult. This study aimed to predict lethal pulmonary hypoplasia in patients with CDH prior to ECMO.

Methods This was a multicenter cohort study involving neonates prenatally diagnosed with isolated unilateral CDH (born 2006–2020). Patients who required ECMO due to respiratory insufficiency were included in this study. Patients who underwent ECMO due to transient disorders were excluded from analysis. Blood gas analysis data within 24 h of birth were compared between survivors and non-survivors. Predictive abilities were assessed for factors with significant differences.

Results Overall, 34 patients were included (18 survivors and 16 non-survivors). The best pre-ductal PaO_2 was significantly lower in non-survivors than in survivors (50.4 [IQR 30.3–64.5] vs. 67.5 [IQR 52.4–103.2] mmHg, respectively; $p = 0.047$). A cutoff PaO_2 of 42.9 mmHg had a sensitivity, specificity, and positive predictive value of 50.0%, 94.4%, and 88.9%, respectively, to predict mortality.

Conclusion The best PaO_2 within 24 h after birth predicted mortality following ECMO initiation. This should be shared to families and caregivers to optimize the best interests of the infants with CDH.

Keywords Extracorporeal membrane oxygenation · Congenital diaphragmatic hernia · Congenital abnormalities · Blood gas analysis · Palliative care · Neonatal intensive care

Introduction

Persistent pulmonary hypertension of the newborn in patients with congenital diaphragmatic hernia (CDH) remains one of the most challenging neonatal conditions. Several therapeutic modalities, including high-frequency oscillatory ventilation, nitric oxide inhalation, and extracorporeal membrane oxygenation (ECMO) improve mortality and morbidity in patients with CDH [1–3]. ECMO is the ultimate life-saving rescue therapy for cardiorespiratory insufficiency. The purpose of ECMO in CDH patients is not to cure pulmonary hypoplasia, but to serve as a bridge therapy until the underlying heart and lung pathology is corrected [4]. However, in some cases, pulmonary hypoplasia is so severe that, despite treatment, patients cannot be weaned from ECMO. Although the identification of patients with lethal pulmonary hypoplasia would allow a better palliative care and more efficient allocation of finite medical resources, no tool exists to this purpose yet.

In this regard, the Severe Pulmonary Hypoplasia and Evaluation for Resuscitative Efforts (SPHERE) protocol (developed at Mott Children's Hospital, University of Michigan) aimed to identify patients with lethal pulmonary hypoplasia using blood gas analysis (BGA) within hours of birth [5]. This protocol, which was devised based on opinions from experts in tertiary academic institutions, could not predict mortality in the registry data of the Congenital Diaphragmatic Hernia Study Group (CDHSG) [6].

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The aim of this study was to predict lethal pulmonary hypoplasia in CDH patients prior to ECMO using the Japanese Congenital Diaphragmatic Hernia Study Group (JCDHSG) database.

Methods

Study design and patient selection

The JCDHSG has conducted a multicenter cohort study that had a retrospective design from 2006 to 2016, and is currently being continued by a prospective cohort study since 2017. Its database includes infants with CDH who were diagnosed prenatally or within 28 days after birth and were hospitalized in the 15 participating centers between January 2006 and December 2020.

In the present study, we reviewed the JCDHSG database and selected patients who had a prenatal diagnosis of unilateral CDH, were born at a gestational age ≥ 34 weeks, and required ECMO. Patients with life-limiting chromosomal abnormalities, such as trisomy 13 or 18, or severe cardiac malformations that affected respiratory management were excluded. Additionally, to focus exclusively on lethal pulmonary hypoplasia, patients who underwent ECMO due to pneumothorax, transient airway disorders including tracheal bleeding and sputum retention, or congenital tracheal stenosis were excluded. Finally, patients with missing data on pre-ductal BGA or prognosis at 90 days of life were also excluded from analysis.

In all participating centers, patient management was based on the same therapeutic protocol since 2017. ECMO indication and timing, as well as surgery timing were decided based on each institution's criteria.

Variables

The following variables were extracted from the JCDHSG database: sex, gestational age, birth weight, CDH side, observed/expected lung area-to-head circumference ratio (o/eLHR) [7], liver-up [8], thoracic position of the stomach [9], Apgar score at 1 and 5 mins, umbilical arterial blood gas data (pH, base excess, PaO_2, and $PaCO_2$), international classification of the diaphragmatic defect [10], best pre-ductal PaO_2 and $PaCO_2$ within 24 h after birth, best oxygenation index (OI) calculated using the best PaO_2 and the ventilator settings at time of blood sampling, age at ECMO initiation, duration and type of ECMO, and timing of surgery. If the o/eLHR was measured more than once, the minimum value was used. Liver-up was defined as a prenatally detected liver herniation occupying more than one-third of the thoracic space. The position of the stomach was categorized as follows: grade 0, abdominal; grade 1, left thoracic; grade 2, less than half of the stomach herniated into the right chest, and grade 3, more than half of the stomach herniated into the right chest [9]. Liver-up and the position of stomach were only counted in patients with left CDH.

Prediction of lethal pulmonary hypoplasia

"Lethal pulmonary hypoplasia" was defined as patients with CDH who did not survive despite treatment with ECMO. Patients were dichotomized based on whether they survived or not at 90 days of age. BGA data within 24 h after birth were compared between survivors and non-survivors. In case of a significant difference, a cutoff value was calculated using a receiver operating characteristic (ROC) curve. The predictive ability of the cutoff value, including the area under the ROC curve, sensitivity, specificity, and positive predictive value were also assessed.

Statistical analysis

Summary statistics were expressed as frequencies and proportions for categorical data and median and interquartile range (IQR) for continuous variables. Statistical comparisons between the two groups were performed using the Wilcoxon signed-rank test for continuous variables and the chi-square or Fisher's exact tests for categorical variables. Areas under the ROC curve (that is, the C-index) were constructed to assess the discriminatory power of each of the risk factors. The optimal cut-off value was determined by maximal Youden index. Statistical significance was defined as two-sided $p < 0.05$. All statistical analyses were performed using JMP software (version 12.01; SAS Institute, Inc., Cary, NC, USA).

Ethical approval

This study was approved by the Ethics Committee of Chiba University Hospital (approval number 509). The requirement for signed informed consent was waived because of the retrospective study design and the use of de-identified data. Details of the study were published on an institutional website, and individuals had the right to decline participation. The study was performed in accordance with the principles of the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

Results

Baseline characteristics

Overall, 1037 patients were included in the JCDHSG database during the study period. In these, 70 (7%) patients with

CDH underwent ECMO. From the 15 participating institutions, ECMO was exclusively performed in 8 institutions (median of 7 [IQR 5–10] cases per institution). Fifteen patients were excluded due to missing data on BGA and/or 90-day prognosis, three due to postnatal diagnosis of CDH, and one due to gestational age <34 weeks. Two patients were excluded because they presented bilateral CDH and ten due to life-limiting chromosomal abnormalities and/or severe cardiac malformations. Additionally, we excluded 16 patients who underwent ECMO due to additional reasons (pneumothorax, $n = 10$; transient airway disorder, $n = 2$; congenital tracheal stenosis and unilateral pulmonary aplasia, $n = 1$; and cardiac failure, $n = 3$).

Finally, 34 patients were eligible for analysis, of which 18 had survived and 16 had died at 90 days of age; Table 1 shows a comparison of demographic data between these 2 groups. There was no difference between survivors and non-survivors in the prenatal prediction of severity and other potential risk factors. Non-survivors had a lower surgery rate (69 vs. 100%, $p = 0.016$) and longer ECMO duration (9 vs. 6 days, $p = 0.035$) than survivors.

Differences in BGA between survivors and non-survivors

Figure 1 shows a comparison of BGA data within 24 h after birth. Non-survivors had a significantly lower best PaO_2 (50.4 [IQR 30.3–64.5] vs. 67.5 [IQR 52.4–103.2] mmHg, $p = 0.047$) and higher best OI (33.4 [IQR 23.3–59.1] vs. 19.5 [IQR 14.9–27.4], $p = 0.0338$) than survivors. In contrast, the best $PaCO_2$ was not significantly different among groups (38.7 [IQR 27.8–51.8] vs. 31.9 [IQR 28.6–63.9] mmHg, $p = 0.823$).

Prediction of lethal pulmonary hypoplasia

The optimal cutoff values of best PaO_2 and OI were 42.9 mmHg and 23.2, respectively. The ability of these parameters to predict mortality is shown in Table 2. The C-index of best PaO_2 and OI were 0.70, and 0.72, respectively. The positive predictive values of the best PaO_2 and OI were 88.9% and 68.4%, respectively.

Table 1 Comparison of baseline characteristics between survivors and non-survivors

Variables	Survivors ($n = 18$)	Non-survivors ($n = 16$)	p value
Gestational age (weeks)	37.4 (37.1 to 38.2)	37.2 (36.7 to 37.5)	0.107
Birth weight (g)	2888 (2564 to 2964)	2716 (2463 to 2947)	0.277
Male sex	7/18 (39)	8/16 (50)	0.515
Left CDH	17/18 (94)	15/16 (94)	1.000
Diaphragmatic defect type C or D	15/18 (83)	8/11 (73)	0.646
o/eLHR	27.9 (23.3 to 39.9)	29.9 (15.5 to 40.4)	0.909
Liver-up	8/17 (47)	11/15 (73)	0.166
Grade-3 stomach position	6/17 (35)	7/15 (47)	0.720
UA-BGA, pH	7.34 (7.3 to 7.36)	7.33 (7.31 to 7.34)	0.661
UA-BGA, Base Excess	− 2.1 (− 3.3 to − 1.2)	− 0.4 (− 2.9 to 0.2)	0.153
UA-BGA, $PaCO_2$ (mmHg)	45.8 (41.7 to 48.6)	48.7 (41.1 to 51.4)	0.563
UA-BGA, PaO_2 (mmHg)	24.3 (16.9 to 26.3)	22.9 (18.6 to 26.3)	0.969
Apgar score at 1 min	4 (2 to 6)	3 (1 to 5)	0.402
Apgar score at 5 min	4 (3 to 5)	4 (3 to 6)	1.000
ECMO initiation (day of age)	1 (0 to 1)	0 (0 to 1)	0.121
ECMO duration (days)	6 (5 to 9)	9 (7 to 13)	**0.035**
V-A ECMO	12/18 (67)	11/16 (69)	0.897
Surgery	18/18 (100)	11/16 (69)	**0.016**
Surgery on ECMO	7/18 (39)	7/11 (64)	0.194

Liver-up was defined as a prenatally detected liver herniation occupying more than one-third of the thoracic space. Grade-3 stomach position represents more than half of the stomach herniated into the right chest. Liver-up and the position of stomach were only counted in patients with left CDH. Data are expressed as median (interquartile range) or n (%). P-value < 0.05 was significant (in bold)

CDH congenital diaphragmatic hernia, *o/eLHR* observed/expected lung area-to-head circumference ratio, *UA-BGA* umbilical arterial blood gas analysis, *ECMO* extracorporeal membrane oxygenation, *V-A ECMO* veno-arterial ECMO

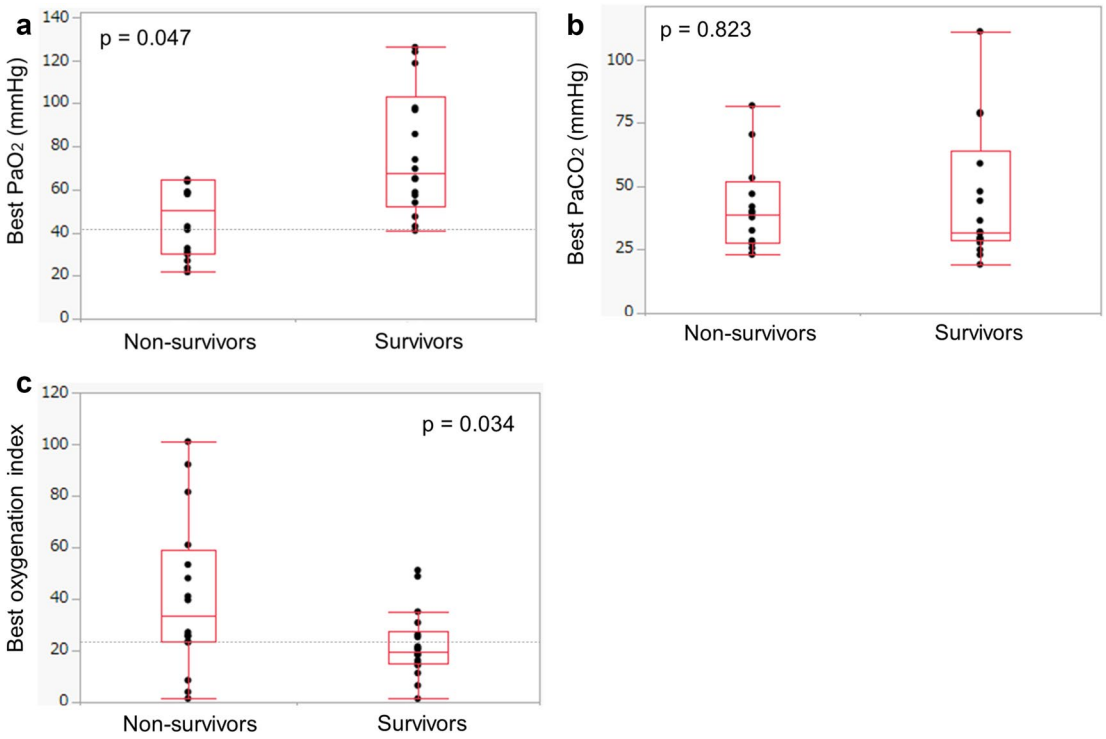

Fig. 1 Box-and-whisker plots of the best PaO_2 (**a**), $PaCO_2$ (**b**), and oxygenation index (**c**) in non-survivors and survivors. The horizontal lines, box length, and whiskers represent the median values, interquartile ranges, and maximum and minimum ranges (except outliers), respectively. Broken lines represent the cutoff values. Outliers in the best PaO_2 and $PaCO_2$ figures are omitted for convenience

Table 2 Ability of the best pre-ductal PaO_2 and oxygenation index to predict mortality

Variables	Best pre-ductal PaO_2 < 42.9 mmHg	Best pre-ductal oxygenation index ≥ 23.2
C-index	0.70	0.72
Sensitivity	50.0%	81.3%
Specificity	94.4%	66.7%
Positive predictive value	88.9%	68.4%
Negative predictive value	68.0%	80.0%

Discussion

In this study, we found that the best pre-ductal PaO_2 and OI predicted survival in patients with CDH who underwent ECMO. In particular, the PaO_2 cutoff value of 42.9 mmHg showed a sufficiently high positive predictive value (88.9%) to constitute a potential screening tool for lethal pulmonary hypoplasia prior to ECMO initiation.

Despite the benefits of ECMO [11], patients with severe CDH present a remarkably poor prognosis. According to the Extracorporeal Life Support Organization registry between 2010 and 2016, the survival rate of patients with CDH and pulmonary hypoplasia was 42% [12]. Although reasons behind this unsatisfactory high mortality rate are complex [13], therapeutic outcomes have been associated with institutional experience [14] and duration of ECMO [15]. In addition to these, we think that including patients with lethal pulmonary hypoplasia as ECMO candidates has contributed to the high overall mortality. This concern has prompted the conduction of the present study.

Although relative contraindications to initiating ECMO support in patients with CDH include significant congenital anomalies, grade III/IV intraventricular hemorrhage, weight < 2 kg, and gestational age < 34 weeks [13], no reliable predictors of poor prognosis in ECMO candidates have been described to date [15]. As mentioned in the Introduction, the SPHERE protocol aimed to predict lethal pulmonary hypoplasia in a select cohort of patients with prenatal suspicion of critical pulmonary hypoplasia. If the infant was unable to maintain a pH > 7.0, $PaCO_2 \leq 100$ mmHg, pre-ductal $SaO_2 \geq 80\%$, and $PaO_2 \geq 40$ mmHg on maximal ventilator support utilizing the maximum settings with appropriate sedation and optimization of blood pressure during the first 2 h of life, or if the infant was clearly moribund or coding, redirection of goals of care to comfort was strongly considered. However, if the baby met these criteria at any point during the first 2 h of observation, ECMO cannulation was performed [5]. Although the SPHERE protocol resulted in more efficient resource use when considering institutional

data, analysis of the CDHSG database revealed that survival rates were not significantly different between patients with a best $PaCO_2 \leq 100$ and those with values > 100 mmHg [6]. Given that this parameter was also not associated with mortality in the present study, the $PaCO_2$ does not seem to be useful to identify which patients will benefit from ECMO.

In contrast, a PaO_2 of < 42.9 mmHg had an excellent positive predictive value in predicting mortality in our study. Furthermore, PaO_2 of <40 mmHg factor proposed in the SPHERE protocol had a positive predictive value of 100% in our cohort as shown in Fig. 1a). Although the best OI also exhibited good predictive ability, its lower positive predictive value compared to PaO_2 makes it a less convenient option. Therefore, we believe that the best pre-ductal PaO_2 could represent a valuable screening tool that minimizes false positivity when detecting lethal pulmonary hypoplasia.

Another advantage of this study is that it focused on precise data derived from an overall homogeneous, selected population. In the JCDHSG study, we had already investigated ECMO use in a Japanese registry data from 2006 to 2010, and compared the best PaO_2 and $PaCO_2$ prior to ECMO initiation between survivors and non-survivors [3]. However, in the current study, we focused on detecting lethal pulmonary hypoplasia. Therefore, by excluding patients who had required ECMO due to transient disorders (such as pneumothorax and airway problems), we were able to examine the more genuine effect of pulmonary hypoplasia associated with CDH. Furthermore, only pre-ductal BGA data (which are better than post-ductal data under pulmonary hypertension status) were used for analyses.

Although the topic was originally controversial [16], several guidelines for palliative care in neonates are now available in various regions nowadays [17]. According to the latest statement of the American College of Obstetricians and Gynecologists (ACOG), "perinatal palliative care refers to a coordinated care strategy that comprises options for obstetric and newborn care that include a focus on maximizing quality of life and comfort for newborns with a variety of conditions considered to be life-limiting in early infancy" [18]. Japanese guidelines in this regard [19], which have been available since 2004, emphasize that determination of the course of medical treatment must be based on the "best interests of the child." The following statement from the ACOG [18] is helpful to clarify this concept: "Decisions about non-initiation or withdrawal of intensive care should be made by the health care team and the parents of a high-risk infant working together. This approach requires an honest and open communication. Ongoing evaluation of the condition and prognosis of high-risk infants is essential, and the physician, as the spokesperson for the health care team, must convey this information accurately and openly to the parents of the infant." Considering this, we hope that the results of our study will be useful for assessing prognosis more accurately and help the shared decision-making process of parents and caregivers.

The current study had several limitations. First, due to its multicenter design, therapeutic strategies were not uniform until 2017. Second, the sample size was relatively small. This is because: (1) ECMO use has not been widespread in Japan [3], and (2) as explained above, our selection criteria were strict, which enabled a more precise and specific analysis. Third, we excluded patients with pneumothorax in this study, which might have resulted in excessive exclusion because there might be unavoidable, non-treatment-related pneumothorax due to pulmonary hypoplasia. Fourth, the cut-off value presented in this study may not be used for screening lethal pulmonary hypoplasia in every infant, but only in those with severe CDH diagnosed prenatally, as described in the SPHERE protocol. Fifth, the C-index of best PaO_2 and OI were not sufficiently high, therefore, it is still difficult to perfectly predict mortality prior to ECMO. Instead, a high positive predictive value was emphasized in this study to screen lethal pulmonary hypoplasia. Finally, a prospective study is required to validate our results and confirm the prognostic value and applicability of pre-ductal PaO_2 as a screening tool.

In conclusion, this study showed that, in infants with CDH, the best PaO_2 and OI within 24 h after birth predicted mortality following ECMO initiation. Particularly, a PaO_2 value of 42.9 mmHg had a sufficiently high positive predictive value. This should be shared to families and caregivers to optimize the best interests of the children in this group.

Author contributions K.T. designed the study and wrote the initial draft of the manuscript. T.F., K.N., S.A., A.Y., K.M., M.Y., T.O., K.U., and M.O. contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript. M.H., H.O., N.I., K.T., and N.U. served as scientific advisors and critically reviewed the study proposal. Y.S. performed the statistical analyses. All other authors contributed to the data collection, interpretation, and critical review of the manuscript. The final version of the manuscript has been approved by all authors.

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Code availability The datasets used in the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was approved by the Ethics Committee of Chiba University Hospital (approval number 509). The study was performed in accordance with the principles of the Declaration of Helsinki and the ethical guidelines for medical and health research involving human subjects.

Informed consent The requirement for signed informed consent was waived because of the retrospective study design and the use of de-identified data. Details of the study were published on an institutional website, and individuals had the right to decline participation.

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