의학석사 학위논문

Respiratory Severe Score as a Predictive Factor for the Mortality of Congenital Diaphragmatic Hernia

선천성 횡격막 탈장의 사망률에 대한 예측 인자로서의 Respiratory Severity Score

2018 년 8 월

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안 자 혜

A thesis of the Master’ s degree

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ABSTRACT

Respiratory severity score as a predictive factor for the mortality of congenital diaphragmatic hernia

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Background: Congenital diaphragmatic hernia (CDH) is rare but potentially fatal. The overall outcome is highly variable. This study aimed to identify a simple and dynamic parameter that helps predict the mortality of CDH patients in real time without invasive tests.

Methods: We conducted a retrospective chart review of 59 CDH cases. Maternal and fetal information included the gestational age at diagnosis, site of defect, presence of liver herniation, and lung-to-head ratio (LHR) at 20-29 weeks of gestational age. Information regarding postnatal treatment, including the number of days until surgery, the need for inhaled nitric oxide (iNO), the need for extracorporeal membrane oxygenation (ECMO), and survival, was collected. The highest respiratory severity score (RSS) within 24 h after birth was also calculated.

Results: Statistical analysis showed that a younger gestational age at initial diagnosis ($P < 0.001$), a lower LHR ($P = 0.001$), and the presence of liver herniation ($P = 0.003$) were prenatal risk factors for CDH mortality. The highest RSS within 24 h after birth and use of iNO and ECMO were significant factors affecting survival. In the multivariate analysis, the only remaining significant risk factor was the highest preoperative RSS within 24 h after birth ($P = 0.002$). The area under the ROC curve was 0.9375 with a sensitivity of 91.67% and specificity of 83.87% at the RSS cut-off value of 5.2. The positive and negative predictive values were 82.14% and 92.86%, respectively.

Conclusion: Using the RSS as a prognostic predictor with simple calculations will help clinicians plan CDH patient management.

Keywords: Respiratory severity score, Congenital diaphragmatic hernia, Predictive factor, Mortality, Prognosis, Neonate

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is rare but potentially fatal and affects neonates in 1 out of every 3,000 live births.[1] The severity of pulmonary hypertension due to pulmonary hypoplasia is the major factor determining mortality and morbidity in cases of this disease. Because the overall outcome is highly variable, the management plan is not uniform.[2] There have been many efforts to predict the postnatal outcomes of CDH so that risk stratification can direct the planning of tailored management strategies.[2-6] However, these predictive models are difficult to apply, too complex to understand intuitively and are not able to reflect postnatal progress in real time. Our study began with the design of a simple and dynamic parameter that reflects postnatal changes of CDH patients in real time without a blood test or echocardiogram.

The purpose of the present study was to identify risk factors for predicting the mortality of neonates with CDH. We aimed to address this goal using the respiratory severity score (RSS), which is the product of the mean airway pressure (MAP) and the fraction of inspired oxygen (FiO_2). The RSS was first described in 2004 as an index for noninvasive assessment of ventilatory status.[7] The RSS has been used in clinical trials as a modified surrogate of the oxygenation index (OI, $FiO_2 \times MAP \times 100/PaO_2$),[7-10] and a strong association between the RSS and the OI in ventilated newborns was demonstrated in one study.[11]

METHODS

Seoul National University Children's Hospital (SNUCH) is a tertiary hospital in Seoul, Korea. We have 40 beds in the neonatal intensive care unit (NICU), and approximately 600 neonates are admitted every year. Support from pediatric professionals, including subspecialties and surgeons, is well available for medical interventions or surgery. SNUCH is a high-volume case center (annual repair case number > 6), as per a study that reported the effect of hospital case volume on the outcome of CDH.[12)]

We conducted a retrospective chart review of CDH cases admitted between December 2006 and June 2015. All live inborn and outborn infants with CDH admitted to the NICU of SNUCH within 24 h after birth were included.

The acute postnatal management protocol was as follows. All newborns diagnosed with CDH prenatally were delivered with attending pediatric doctors. Immediate intubation was performed after birth, and mechanical ventilator support was initiated using either the conventional or the high-frequency oscillatory ventilation mode at the NICU. The target range of oxygen saturation was 85 – 95% by pulse oximetry.[13)] We clinically assessed the possibility of pulmonary hypertension in patients with a pre- and postductal SpO_2 saturation difference of ≥ 10%. Echocardiograms were performed before and after surgery to assess the degree of pulmonary hypertension. The diagnostic criteria for pulmonary hypertension were: (1) tricuspid valve regurgitation velocity ≥ 3 m/s in the absence of pulmonary stenosis, (2) flat or left-deviated interventricular septal shape, and (3) right-to-left shunt or right-to-left dominant bidirectional shunt flow through the patent

ductus arteriosus.[14] Patients were classified into 3 groups according to estimated pulmonary arterial pressure (PAP) relative to systemic systolic blood pressure: PAP less than 2/3 of systemic systolic pressure (no/mild pulmonary hypertension), PAP equal to or greater than 2/3 of systemic-to-systemic pressure (moderate pulmonary hypertension), or PAP indicating systemic-to-suprasystemic pressure (severe pulmonary hypertension). The assessment hierarchy was: (1) pressure differential by direction and velocity of ductus arteriosus flow using the Bernoulli equation; (2) 2-dimensional interventricular septum position (parasternal short axis), graded as normal, flattened (indicating right ventricular pressure ≥ 2/3 systemic pressure), or D-shaped (right ventricular pressure considered to be systemic-to-suprasystemic pressure); and (3) right ventricular pressures based on peak tricuspid valve regurgitation (TR) jet velocity estimated by the modified Bernoulli equation (assuming a right atrial pressure of 0 mmHg).[15, 16]

We applied inhaled nitric oxide (iNO) therapy to infants with pulmonary hypertension if they showed evidence of extrapulmonary right-to-left shunting and if the OI turned out to be greater than 25 after effective lung recruitment.[13, 17] The usual starting dose was 20 ppm. Additionally, hemodynamic support comprising volume expansion or the administration of catecholamines was conducted when necessary. We performed an extracorporeal membrane oxygenation (ECMO) procedure if a patient with pulmonary hypertension did not respond to medical therapy or if the OI was elevated above 40,[18-20] except when the patient was less than 34 weeks of gestational age or weighed less than 2 kg. Other indications for ECMO included increased $PaCO_2$ and refractory respiratory acidosis with pH < 7.15. Usually, we preferred immediate (< 24 h after birth)

repair after initial stabilization with a gentle ventilation technique rather than delayed (> 48 h after birth) repair of CDH because no known definitive benefit of prolonged stabilization of CDH patients before repair surgery has been demonstrated to date.[21, 22] Repair surgery was performed in patients on ECMO in some cases.

The variables collected for analysis included gestational age, birth weight, sex, and other combined anomalies. Additionally, maternal information was collected. Data included demographics, antenatal history, mode of delivery, and fetal information, including the gestational age at CDH diagnosis, the site of defect, the presence of liver herniation, and the lung-to-head ratio (LHR), which was included only if the measurement was taken from a sonogram that had been performed at 20-29 weeks of gestational age. The collected information regarding postnatal treatment included the number of days until surgery, the need for iNO, the need for ECMO, and survival. The RSS (MAP × FiO_2) was calculated hourly during the 24 h after birth. If the conventional ventilation mode was used, the MAP was calculated as MAP = PEEP + [(PIP-PEEP) × (t_i/t_i+t_e)] (PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; t_i, inspiratory time; t_e, expiratory time).[23] If the high-frequency oscillatory ventilation mode was applied, the MAP of the actual ventilator setting was used for calculating RSS.

Statistical analysis

Demographic data and previously published predictors of the outcome were examined by univariate analyses with independent *t*-tests and Wilcoxon rank-sum tests. The χ^2 test was used to evaluate categorical data, and the Mann-Whitney *U*-test was used for all comparisons of continuous variables. Any value of $P < 0.05$

was considered statistically significant. Factors thought to be useful for the pretreatment stratification scheme were examined with multivariate logistic regression analyses. Cox proportional hazards multivariate models were generated to assess the relationships between the risk factors of CDH and mortality. Area under the receiver operating characteristic (ROC) curve (AUC) analysis was used to determine the cut-off value of the predictive factor. Data were described as the mean ± the standard deviation (SD) and the range or as rates. All statistical analyses were performed using SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA) and STATA ver. 12.1 (STATA Corp., College Station, TX, USA).

Ethics statement

The study was approved by the institutional review board of SNUCH (IRB No. 1804-084-937).

RESULTS

A total of 59 infants who were diagnosed with CDH and admitted to the NICU during the study period were included in the analysis. A flowchart of the disease course is presented in Figure 1. Preoperative ECMO was performed in 5 patients, and among them, 1 patient also underwent postoperative ECMO. One patient who underwent ECMO but not surgery expired. All 13 patients without surgical intervention died, regardless of whether ECMO was performed. Specifically, they could not have surgery because their general condition was not favorable to operation and not improved, thus finally expired. Diaphragmatic hernia repair was performed in 46 neonates, and the number of survivors was 34.

The baseline characteristics of the patients are shown in Table 1. The mean gestational age was 38.71 ± 1.43 weeks, and the mean birth weight was 3,001 ± 510 g.

First, we analyzed the presumptive prenatal risk factors for CDH mortality. The results of the statistical analysis indicated that a younger gestational age at initial diagnosis ($P < 0.001$), a lower LHR ($P = 0.001$), and the presence of liver herniation ($P = 0.003$) were significantly associated with CDH mortality in the study. The differences in these factors between the survival group and the death group are presented in Table 2.

Possible postnatal risk factors for CDH, including hernia repair surgery, the number of days from birth to the day of surgery, the highest preoperative RSS within 24 h after birth, the highest postoperative RSS within 24 h after surgery, the application of preoperative and postoperative inhaled NO, and the application of preoperative

and postoperative ECMO, are compared in Table 3. All survivors had repair operations. Additionally, the RSS and the application of iNO and ECMO were factors that significantly affected the survival rate.

Multivariate analysis was performed using the aforementioned statistically significant factors. The only remaining factor significantly affecting CDH mortality in this analysis was the highest preoperative RSS within 24 h after birth (P = 0.002) (Table 4).

ROC analysis of the preoperative RSS was performed to identify the appropriate cut-off value to predict mortality (Figure 2). The AUC was 0.9375 with a sensitivity of 91.67% and a specificity of 83.87% at a cut-off value of 5.2. The positive and negative predictive values were 82.14% and 92.86%, respectively.

Fig. 1. Flowchart of disease course in patients admitted between December 2006 and June 2015.

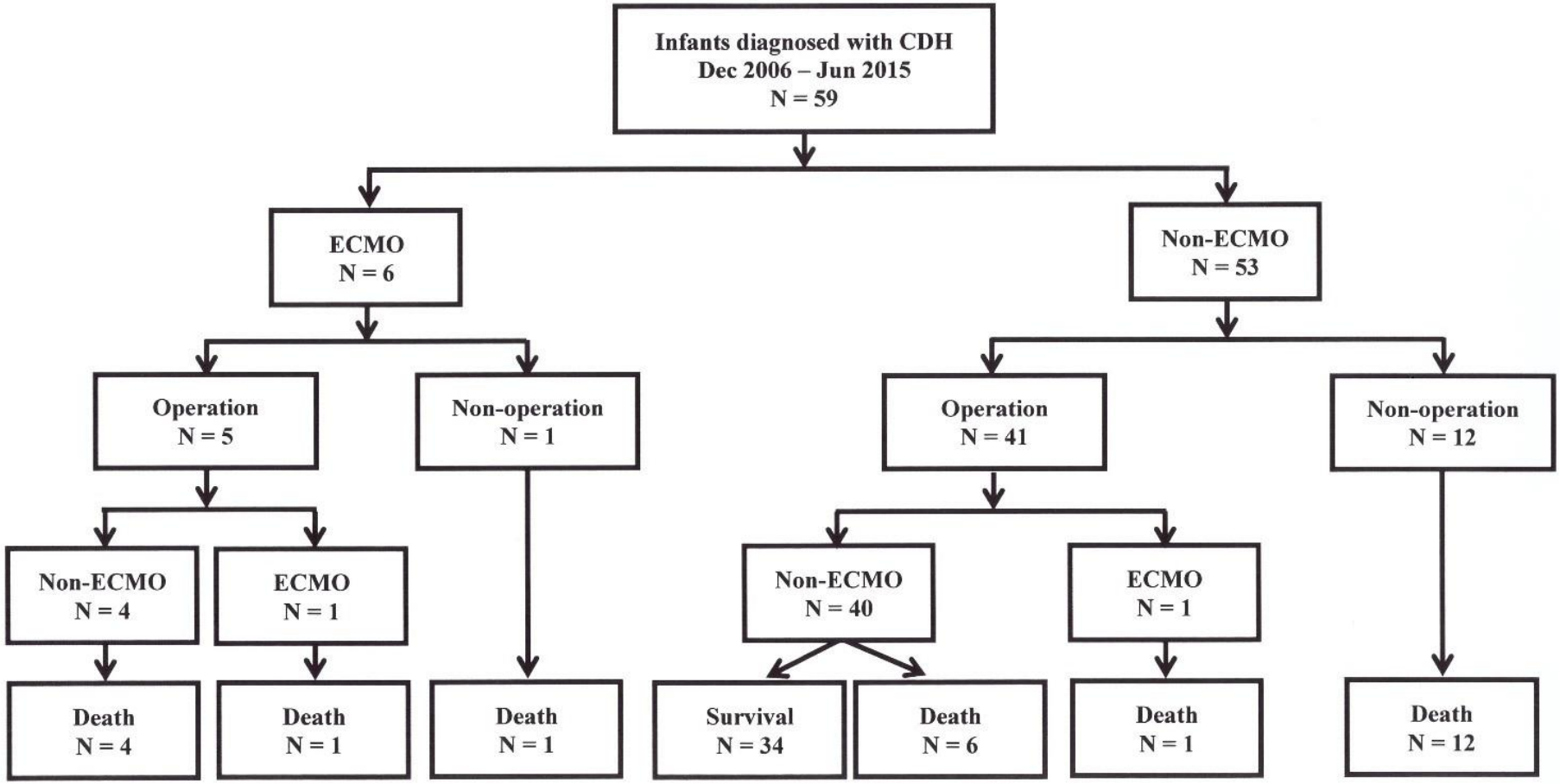


Table 1. Baseline characteristics of studied infants with congenital diaphragmatic hernia. (n = 59)

		Mean ± SD (range) or Number (%)
Gestational age (weeks)		38.71 ± 1.43 (34 to 41.43)
Birth weight (grams)		3001 ± 510 (1570 to 3900)
Male		39 (66.1%)
Small for gestational age (< 10%)		15 (25.4%)
Duration of assisted ventilation (days)	**Survival (n = 34)**	13.68 ± 17.31 (3 to 104)
	Death (n = 25)	8.16 ± 8.16 (0 to 28)
Duration of hospitalization (days)	**Survival (n = 34)**	27.29 ± 23.35 (10 to 131)
	Death (n = 25)	8.2 ± 8 (1 to 28)

Data were described as the Mean ± SD (range) or Number (%)

Table 2. Prenatal risk factors for the mortality of congenital diaphragmatic hernia.

Mean ± SD (range) or Number (%)	Survival (n = 34)	Death (n = 25)	*P* - value
Gestational age (weeks)	38.86 ± 1.14	38.71 ± 1.86	0.884
Birth weight (grams)	3073.82 ± 447.38	2898.33 ± 581.85	0.398
SGA	8 (23.5%)	7 (28%)	0.763
Initial diagnosis (weeks)	28.43 ± 5.57	19.71 ± 9.86	< 0.001
LHR	2.15 ± 0.99	1.26 ± 0.63	0.001
Site (right side)	0 (0%)	3 (12%)	0.071
Liver herniation	11 (32.4%)	17 (68%)	0.003
Combined anomaly	4 (11.8%)	7 (28%)	0.172
Complex heart disease	2 (5.9%)	1 (4%)	1.000

Abbreviations: SGA, small for gestational age; LHR, lung-to-head ratio.

Table 3. Postnatal risk factors for the mortality of congenital diaphragmatic hernia.

Mean ± SD (range) or Number (%)	Survival (n = 34)	Death (n = 25)	*P* - value
Operation	34 (100%)	12 (48%)	0.001
Operation day	2.74 ± 2.88	4.25 ± 2.99	0.117
The highest preoperative RSS within 24 h after birth	3.99 ± 2.21	14.50 ± 5.33	< 0.001
Preoperative NO	6 (17.6%)	24 (96%)	< 0.001
Preoperative ECMO	0 (0%)	6 (24%)	0.004
The highest postoperative RSS within 24 h after surgery	3.98 ± 1.94	12.32 ± 10.61	0.004
Postoperative NO	7 (20.6%)	11 (44%)	< 0.001
Postoperative ECMO	0 (0%)	6 (24%)	< 0.001

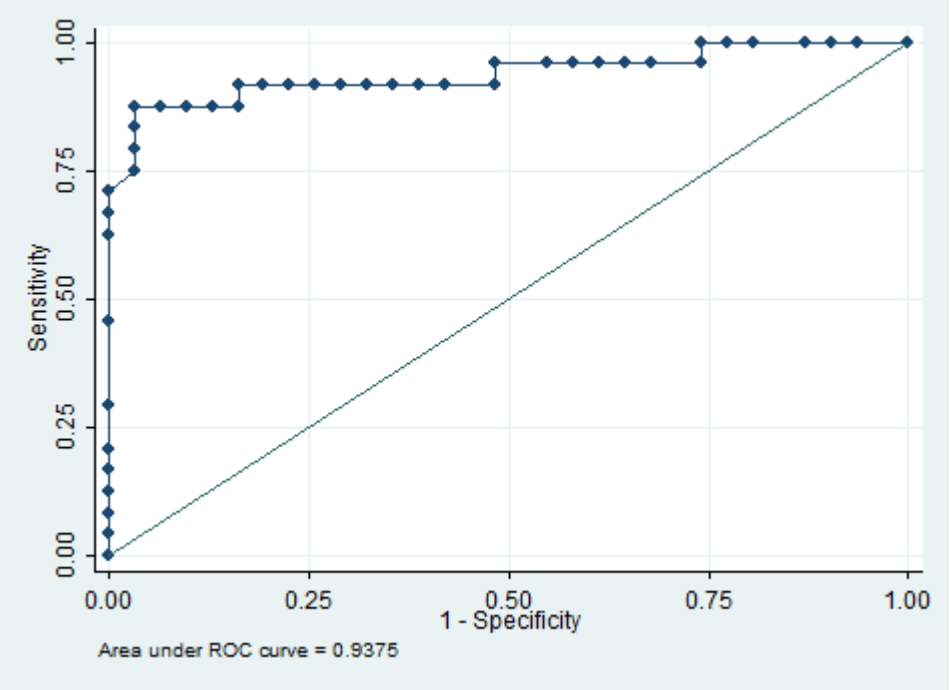
Abbreviations: RSS, respiratory severity score; NO, nitric oxide; ECMO, extracorporeal membrane oxygenation.

Table 4. Risk factors for the mortality of congenital diaphragmatic hernia assessed by multivariate analysis.

	***P* - value**	**OR (95% CI)**
GA with initial diagnosis	0.061	0.964 (0.928, 1.002)
LHR	0.249	0.375 (0.071, 1.989)
The highest preoperative RSS within 24 h after birth	0.002	1.591 (1.181, 2.145)
Liver herniation	0.195	0.169 (0.012, 2.487)

Abbreviations: GA, gestational age; LHR, lung-to-head ratio; RSS, respiratory severity score; OR, odds ratio; CI, confidence interval.

Fig. 2. Receiver operating characteristic curve of the highest preoperative respiratory severity score within 24 h after birth.



DISCUSSION

To our knowledge, the present study is the first evaluation of the relationship between RSS and CDH. We found that the preoperative RSS within 24 h after birth was the most significant predictive factor; the cut-off value had acceptable sensitivity and specificity values according to the ROC curve analysis for the prognoses of CDH neonates. The positive and negative predictive values were also reasonable. The contribution of this study is the finding and suggesting of a possible postnatal respiratory predictive factor for the prognosis of CDH.

Originally, the RSS was designed under conditions in which PaO_2 measurements were not routinely performed because not all patients had umbilical arterial catheters. Indwelling arterial catheters are required for the frequent monitoring of other respiratory indices, such as OI, and thus, complications including thrombosis and infection are potential burdens.[24, 25] Furthermore, the risk of iatrogenic anemia following blood samplings that often require multiple blood transfusions should be a concern.[26] However, when using the RSS, there is no need to perform frequent blood sampling, and hence, the effort and risk are reduced. Previous studies suggested that using the RSS as a respiratory index can be an option for less invasive intensive care, especially for the most vulnerable patients in the NICU. One study reported that the RSS on day 30 of life can provide useful prognostic information for very low birth weight infants undergoing prolonged mechanical ventilation.[9] Recently, a study addressing RSS and extubation readiness in very low birth weight infants was published.[27] These reports, along with ours, suggest that the RSS can be used as a reliable respiratory predictive factor.

To date, several studies have addressed factors that can predict the prognoses of CDH neonates, but no standardized, universally accepted method has been identified. Known candidate prenatal evaluation factors, such as the gestational age when the initial diagnosis was made, the LHR, and liver herniation, have been proposed. However, these factors are insufficient to reflect the variable changes in the postnatal disease course, because they are fixed values taken at a single moment during the prenatal period. Additionally, another problem exists wherein a measured value, such as the LHR, is originally subjective and operator dependent. Recently, the Congenital Diaphragmatic Hernia Study Group suggested a scoring equation with multiple variables, such as birth weight, Apgar scores, the presence of severe pulmonary hypertension at the first echocardiogram, a major cardiac anomaly, and chromosomal anomaly.[2] However, these are all fixed factors measured at a single evaluation and hence, cannot reflect the dynamic disease course of this group of patients. Conversely, the RSS is the product of 2 real-time values and is thus able to promptly reflect the changing conditions of patients. The values can be objectively measured and easily obtained without any invasive procedure. This is the specific usefulness of the RSS as a dynamic prognostic predictive factor and the strength of the present study.

Although not included in the results, we analyzed the characteristics of patients whose highest preoperative RSSs were higher than the median. The median of the highest RSS within 24 h after birth was 5.053, which is close to the cut-off RSS value of 5.2 determined by the ROC in this study. Of 28 children with an RSS $\geq$ 5.053, only 5 (17.9%) survived, and 23 (82.1%) died. The characteristics of the survivors and of those that died were examined based on factors shown in the

analysis results of Table 2 and Table 3. The factors with significant differences between the two groups were the gestational age when the initial diagnosis was made (P = 0.05), the LHR (P < 0.001), the highest RSS within 24 h after birth (P = 0.001), use of preoperative iNO (P = 0.011), the highest RSS within 24 h after surgery (P = 0.027), the use of postoperative iNO (P = 0.001) and the use of postoperative ECMO (P = 0.044). Thus, we can hypothesize that although the highest RSS within 24 h after birth is greater than the median (RSS = 5.053), the probability of survival would be relatively high if the gestational age at initial diagnosis is older, if the LHR is relatively high, and the highest RSS within 24 h after birth are relatively low.

All neonates who died before surgery had conditions that were not favorable to repair operations. Our results showed significant differences between the survivor and nonsurvivor groups regarding the application of iNO and ECMO. iNO improves oxygenation, and reduces the need for ECMO in neonates with persistent pulmonary hypertension.[28] However, no randomized trial has demonstrated that iNO improves the outcomes of CDH patients. Moreover, 2 well-designed trials found that early iNO treatment fails to improve survival or reduce the need for ECMO in newborns with CDH.[29] Even the possibility of increasing the need for ECMO in CDH patients treated with iNO has been suggested.[30] The poorer outcome in our patients who were treated with iNO could be partially explained by these findings.[31] In another regard, it is possible that patients with a poor condition from birth may have died without improvement after receiving iNO. Comparison of the mean highest RSS within 24 h after birth revealed that patients who were given preoperative iNO had a higher mean RSS (13.01) than those who were not given

preoperative iNO (3.98) ($P < 0.001$).

The benefit of ECMO for CDH patients is still unclear.[18] The benefit of delayed surgery after ECMO rather than emergency surgery during ECMO was reported previously, but there has been no convincing reduction in mortality with ECMO in randomized trials. In our study, all patients who received ECMO either pre- or postoperatively died. As noted, we consider ECMO use mainly if the OI exceeds 40. However, because of the invasiveness of the procedure and known poor long-term outcome,[32] we tend to avoid ECMO use as long as the baby can withstand the disease course. As a result, only the most seriously ill patients who did not respond to other treatments would have been chosen to receive ECMO. Thus, we think that some degree of selection bias affected the higher mortality of the ECMO group. This tendency in treatment strategies was observed in another study in Japan.[33]

The present study may have several limitations because it is based on a retrospective chart review in a single center. Additionally, during the study period, there were quantitative and qualitative changes in the NICU. Therefore, gradual changes in clinical practice over 10 years, such as in the ventilation strategy, treatment of pulmonary hypertension, and timing of surgery may not have been adequately corrected for in the results. A prospective multicenter study with a precisely designed protocol will be needed to address this issue. For examining the clinical utility of RSS in the treatment of CDH, studies about the relation of RSS with long-term outcomes, specifically with complications such as bronchopulmonary dysplasia, need of daily oxygen, neurodevelopmental delay, and growth retardation, would be needed. Furthermore, the high mortality and

morbidity of the CDH patient group arise from refractory pulmonary hypertension. Thus, the medical approach to these patients is mainly focused on treating pulmonary hypertension, which is unavoidably accompanied by pulmonary hypoplasia. Future studies should consider using the RSS to evaluate the efficacies of new therapies, including medicine and ventilator modalities, for refractory pulmonary hypertension in CDH patients.

CONCLUSION

We confirmed that the highest RSS value measured within 24 h after birth is related to the prognosis of CDH. The RSS is an index that can be calculated in real time from the ventilator setting without invasive testing. Therefore, using the RSS as a prognostic predictor with simple calculations may help clinicians plan to manage CDH patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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요약(국문초록)

선천성 횡격막 탈장은 드물지만 치명적일 수 있는 질환으로 다양한 예후를 보인다. 본 연구에서는 침습적 검사 시행의 필요 없이 선천성 횡격막 탈장 환아의 사망률을 실시간으로 예측할 수 있는 간단하고 역동적인 예측 인자를 확인하고자 하였다. 2006 년 12 월부터 2015 년 6 월까지 서울대학교 어린이병원 신생아중환자실에 입원한 59 명의 선천성 횡격막 탈장 환아의 의무기록을 후향적으로 분석한 결과, 최초 진단 당시의 어린 재태 연령 ($P < 0.001$), 낮은 폐면적-두위 비 ($P = 0.001$), 간 탈장의 존재 ($P = 0.003$) 이 사망률에 의미있는 출생 전기 인자로 기능하였다. 또한 Respiratory severity score (RSS, 평균기도압과 흡기산소분율의 곱) 와 흡입용 일산화질소의 적용, 그리고 체외막형 산소화장치의 적용이 생존에 의미있게 영향을 미친 인자로 확인되었다. 다변량분석 결과 출생 24 시간 이내의 수술 전 최고 RSS 값이 선천성 횡격막 탈장 환아의 사망률에 유일하게 의미있는 위험 인자로 나타나, 이에 대한 ROC 곡선을 그렸을 때 절단점 5.2 에서 AUC 0.9375 로, 민감도 91.67%, 특이도 83.87%로 확인되었다. 임상적으로 선천성 횡격막 탈장 환아의 치료 계획을 세울 시에 간단한 계산으로 산출되는 RSS 를 예후인자로 이용하는 것이 도움이 될 수 있을 것이다.

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주요어: 선천성 횡격막 탈장, 호흡 중증도 점수, 신생아, 사망률, 예후

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