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H. 知的財産の出願・登録状況

なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

先天性心疾患を合併した先天性横隔膜ヘルニアに関する検討

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研究要旨

【研究目的】

先天性横隔膜ヘルニア（CDH）は10～35%に心血管奇形（CVM）を合併し、CVMを合併したCDHの予後は、非合併例に比較して不良である。CDHではさまざまな予後予測因子が知られているが、CVM合併例における予後予測因子の報告は少ない 。本研究の目的は、本邦にけるCVM合併CDHの予後及び予後予測因子を検討することである。

【研究方法】

厚生労働省難治性疾患克服研究事業：「新生児横隔膜ヘルニアの重症度別治療指針作成に関する研究」における2次調査の応諾が得られた施設において、2006年1月1日～2010年12月31日にCDHと診断された症例のうちCVM合併症例 について、各施設から得られた調査票をもとに後方視的に検討を行った。また、孤立性のPFO/ASD、PDA合併例は除外した上で、CVM合併症例の生命予後及び生存群、死亡群における患者背景因子、肝脱出の有無、重症CVMの有無等につき比較検討を行った。CVMの重症度は生後血行動態に影響を及ぼしていたものを重症と定義した。

【研究結果】

調査期間中に出生したCDHは614例であった。うちPFO/ASD、PDA合併例31例を除いたCVM合併CDHは77例（12.5%）であった。77例中積極的ケアを受けたのは63例、緩和ケアを受けたのは14例であった。積極的ケアを受けた児の生存率（最終転帰）は26/63(41%)であった。重症CVM合併は、最終転帰・死亡に影響する独立した因子であった（OR 6.39（95% CI：1.87～21.83）であった。

【結論】

CVM合併CDHの生存率は約４割と不良であった。また、生命予後を予測する因子として、CDHの重症度よりもCVMの重症度がより関連性が高いことが示唆された。

A．研究目的

先天性横隔膜ヘルニア（CDH）は横隔膜の先天的欠損により腹部臓器が胸腔へ脱出するために肺低形成を生じ、生後重度の呼吸不全を呈する疾患である。近年、Gentle ventilation、HFOV、ECMO等の周術期管理の進歩によりCDHの治療成績は大幅に改善している。

CDHは先天的な奇形症候群の一部として見られることもあり、CDHの10～35%に心血管奇形(CVM)を合併することが知られている。CVMを合併したCDHの予後は、非合併例に比較して不良であることが報告されているが、本邦における検討はなされていない。また、孤立性のCDHではさまざまな予後予測因子が知られているが、CVM合併例における予後予測因子の報告は少ない 。本研究の目的は、本邦にけるCVM合併CDHの予後及び予後予測因子を検討することである。

B．研究方法

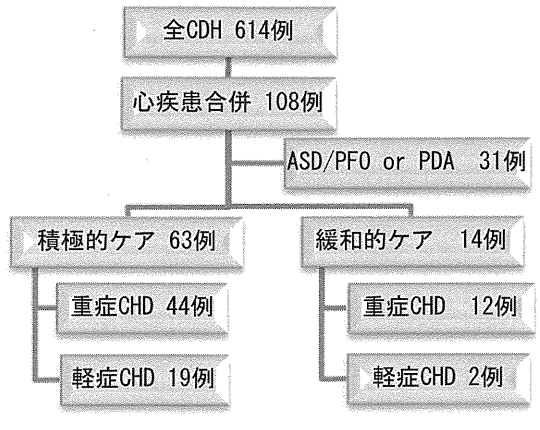
平成 23 年度に日本小児外科学会認定施設・教育関連施設および総合周産期母子医療センターを合わせた159施設を対象としてアンケートによる一次調査を行い、二次調査に関する応諾が得られた 72 施設からのデータをもとに、2006年1月1日～2010年12月31日にCDHと診断された症例のうちCVM合併症例 について、各施設から得られた調査票をもとに後方視的に検討を行った。また、孤立性の卵円孔開存/心房中隔欠損（PFO/ASD)、動脈管開存（PDA）合併例は除外した上で、CVM 合併症例の生命予後及び生存群、死亡群における周産期背景因子、肝脱出、重症 CVM 合併の頻度につき比較検討を行った。CVM の重症度は生後血行動態に影響を及ぼしていたものを重症と定義した。

全ての統計学的解析は統計解析ソフト（Stat Flex for Windows Ver.6.0, Artec, Osaka, Japan）を用いて行った。生存群、死亡群における差の検討は、変数に応じてχ2検定、2標本t検定、マンホイットニー検定を使用した。さらに、生命予後不良の独立した危険因子を検討するために、単変量解析で $p<0.15$ であった変数においてステップワイズ法を用いて変数選択を行い、ロジスティック回帰分析を行った。統計学的有意差は $p<0.05$ とした。

C．研究結果

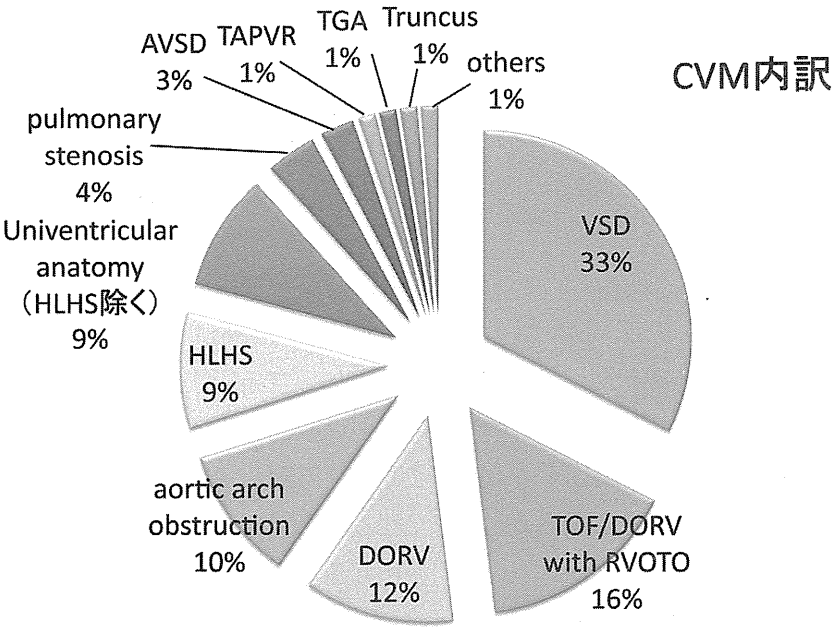
調査期間中に 2 次調査の応諾が得られた72施で出生したCDHは614例であった。うちPFO/ASD、PDA合併例31例を除いたCVM合併CDHは77例（12.5%）であった。77例中積極的ケアを受けたのは63例（軽症CVM合併19例、重症44例)、緩和ケアを受けたのは14例(軽症CVM合併2例、重症12例）であった（図1)。

図1



CVMの内訳は心室中隔欠損症（VSD）(33%)が最多で、ファロー四徴症(TOF)・右室流出路狭窄を伴う両大血管右室起始症(DORV

図２



with RVOTO)(16%)、DORV(12%)、大動脈弓閉塞性疾患(10%)、左心低形成症候群(HLHS)(9%)と続いた（図2)。

生後緩和ケアを受けた14例中12例(86%)が重症CVM合併例であった。また、14例中9例（64%）で13、18トリソミーをはじめとする染色体異常を合併していた。積極的ケアを受けた児の90日生存率は29/63(54%)（重症CVM合併19/44（43%）、軽症15/19（79%））で、調査時生存率は26/63(41%)（重症CVM合併12/44（27%）、軽症14/19（74%））であった（表1)。

生存群、死亡群（調査時）の比較では重症CVM合併頻度が生存群46%、死亡群84%と有意に死亡群で高かった。CDHの予後不良因子とされる肝脱出の有無については、有意差を認めなかった（表2)。

表1

		緩和ケア N=14	積極的ケア N=63
軽症CVM		2/14 (14%)	44/63 (70%)
重症CVM		12/14 (86%)	19/63 (30%)
染色体異常合併		9/14 (64%)	8/63 (13%)
13 or 18 trisomy		8/14 (57%)	6/63 (10%)
90日生存	全	0/14	34/63 (54%)
	重症CVM	0/12	19/44 (43%)
	軽症CVM	0/2	15/19 (79%)
最終転帰・生存	全	0/14	26/63 (41%)
	重症CVM	0/12	12/44 (27%)
	軽症CVM	0/2	14/19 (74%)

表2

	生存 N=26	死亡 N=37	p
在胎週数 wk	37.7±2.0	37.0±2.6	0.324
出生体重 g	2255±513	2382±593	0.379
Apgar score 1分値	3(range: 1-8)	3 (range: 0-8)	0.235
Apgar score 5分値	5 (range: 1-8)	5 (range: 1-8)	0.731
性別 女児	14/26 (54%)	21/37(57%)	0.651
分娩方法 経膣	6/26 (23%)	7/36 (19%)	0.729
出生前診断 有	20/26 (77%)	31/37 (84%)	0.357
L-CDH	24/26(92%)	33/37 (89%)	0.517
肝臓脱出 ※	6/23 (31%)	7/29 (24%)	0.581
重症CVM	12/26 (46%)	32/37(84%)	<0.001

※出生前診断例

また、多重ロジスティック回帰分析において、重症CVMは最終転帰・死亡に関連するする独立した因子であった(OR 6.39 95%CI: 1.87-21.83 p=0.003)（表3)。

表3

最終転帰死亡に影響する因子
-ロジスティック回帰分析-

	Adjusted Odd ratio	95% CI	p
重症CVM	6.39	1.87 - 21.83	0.003
肝脱出	0.56	0.19 - 2.49	0.560

疾患別の生存率としては、大動脈弓閉塞性疾患(75%)、VSD(67%)で高かったが、HLHSでは6例中生存例を認めなかった（表4）。

表4

疾患別予後(積極的ケア群)

N=63	N	生存率(最終転帰)
VSD	21	14 (67%)
TOF/DORV with RVOTO	11	2 (18%)
DORV	6	2 (33%)
aortic arch obstruction	7	5 (75%)
HLHS	6	0
Univentricular anatomy ※	6	3 (50%)
pulmonary stenosis	2	1 (50%)
AVSD	1	0
TAPVR	1	0
TGA	1	1 (100%)

※HLHSを除く

D．考察

CDH における CVM 合併頻度は過去の報告と同様に本邦においても約 10%であった。生存率は４割前後であったが、重症 CVM 合併例では30%弱とさらに低い傾向があった。しかしながら、軽症 CVM 合併例の生存率は約 70%と過去に報告されている弧発性 CDH とほぼ同程度と良好であった。また、CVM 合併 CDH の生命予後を予測する因子として、CDH の重症度よりも CVM の重症度がより関連性が高いことが示唆された。

弧発性CDHでは90日以降の死亡例は少なくなるが、今回の検討では 90 日生存 54%から最終転帰・死亡は41%に低下していた。さらに、重症 CVM 合併例に至っては、43%から27%に低下している。このことは、CVM が CDH の予後に大きく影響していることを示唆している。CVM合併例の中には、2心室修復が不可能な例も含まれていると思われ、CDHに伴う肺高血圧症の残存があった場合、グレン、フォンタン手術の成績に影響を及ぼす可能性もある。今回の調査において、調査時年齢が 1 歳未満の症例も含まれていたことを考えると、今回示された生存率よりもさらに低いことが予測される。

肝脱出の有無は孤立性 CDH において最もよく使用される予後予測因子の一つである。また、低出生体重、低アプガースコア、出生前診断有なども過去の報告では予後不良因子とされているが、今回の検討では予後不良因子とはならなかった。生存、死亡群の比較において、死亡の定義を最終転帰としたことから、より CVM の重症度が強く影響したのかもしれない。今回の結果から、CVM 合併 CDH においては、一般的に使用される CDH の予後予測因子を用いて評価するのではなく、CVM の重症度によって予後を評価する必要があると思われる。

疾患別の予後としては、VSD、aortic arch obstruction など上肢の動脈血酸素飽和度が保たれ、2 心室修復が可能な疾患の予後が比較的良好なことが分かった。また、HLHSは積極的治療にも関わらず 6 例中生存例がなかったことから、胎児診断例では妊娠の中断、生後診断例では緩和医療も選択肢の一つになると思われる。

E．結論

CVM合併CDHは孤立性CDHに比較して予後不良であったが、疾患の重症度、形態によっては孤立性CDHと同等であった。さらに、CVM合併例の生命予後は、CDHの重症度よりもCVMの重症度がより関連性が高いことが示唆された。

F．健康危険情報

該当する健康危険情報はない

G．研究発表

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H．知的財産の出願・登録状況

なし

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Usui N, Kitano Y, Okuyama H, Saito M, Masumoto K, Morikawa N, Takayasu H, Nakamura T, Hayashi S, Kawataki M, Ishikawa H, Nose K, Inamura N, Sago H.	Prenatal risk stratification for isolated congenital diaphragmatic hernia: Results of a Japanese multicenter study.	J Pediatr Surg.	46(10)	1873-1880	2011
Usui N, Kamiyama M, Tani G, Kanagawa T, Fukuzawa M.	Use of the medical information on the Internet by pregnant patients with a prenatal diagnosis of neonatal disease requiring surgey.	Pediatr Surg Int.	27(12)	1289-1293	2011
Usui N, Kitano Y, Okuyama H, Saito M, Morikawa N, Takayasu H, Nakamura T, Hayashi S, Kawataki M, Ishikawa H, Nose K, Inamura N, Masumoto K, Sago H.	Reliability of the lung to thorax transverse area ratio as a predictive parameter in fetuses with congenital diaphragmatic hernia.	Pediatr Surg Int.	27(1)	39-45	2011
Taguchi T, Nagata K, Kinoshita Y, Ieiri S, Tajiri T, Teshiba R, Esumi G, Karashima Y, Hoka S, Masumoto K.	The utility of muscle sparing axillar skin crease incision for pediatric thoracic surgery.	Pediatr Surg Int.	28	In Press (10.1007/s00383-011-3013-2)	2012
Teshiba R, Masumoto K, Esumi G, Nagata K, Kinoshita Y, Tajiri T, Taguchi T, Yamamoto K.	Identification of TCTE3 as agene responsible for congenital diaphragmatic hernia using a high-resolution single-nucleotide polymorphism array.	Pediatr Surg Int.	27(2)	193-198	2011
Esumi G, Masumoto K, Teshiba R, Nagata K, Kinoshita Y, Yamaza H, Nonaka K, Taguchi T.	Effect of insulin-like growth factors on lung development in a nitrofen-induced CDH rat model.	Pediatr Surg Int.	27(2)	187-192	2011
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Kitano Y, Okuyama H, Saito M, Usui N, Morikawa N, Masumoto K, Takayasu H, Nakamura T, Ishikawa H, Kawataki M, Hayashi S, Inamura N, Nose K, Sago H.	Reevaluation of Stomach Position as a Simple Prognostic Factor in Fetal Left Congenital Diaphragmatic Hernia: A Multicenter Survey in Japan.	Ultrasound Obstet Gynecol.	37(3)	277-282	2011
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IV. 研究成果の刊行物・別刷

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Prenatal risk stratification for isolated congenital diaphragmatic hernia: results of a Japanese multicenter study

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Risk stratification;
Prognostic classification;
Multicenter study

Abstract

Background/Purpose: The aim of this study was to establish a prenatal prognostic classification system for risk-stratified management in fetuses with isolated congenital diaphragmatic hernia (CDH).

Methods: A multi-institutional retrospective cohort study of isolated CDH, diagnosed prenatally in fetuses delivered during the 2002 to 2007 period at 5 participating institutions in Japan, was conducted. The risk stratification system was formulated based on the odds ratios of prenatal parameters for mortality at 90 days. The clinical severity in CDH infants were compared among the stratified risk groups.

Results: Patients were classified into the 3 risk groups: group A (n = 48) consisted of infants showing liver-down with contralateral lung–to–thorax transverse area ratio (L/T) ratio ≥0.08; group B of infants showing liver-down with L/T ratio <0.08 or liver-up with L/T ratio ≥0.08 (n = 35), and group C of infants showing liver-up with L/T ratio <0.08 (n = 20). The mortality at 90 days in groups A, B, and C were 0.0%, 20.0%, and 65.0%, respectively. The intact discharge rates were 95.8%, 60.0%, and 5.0%, respectively. This system also accurately reflected the clinical severity in CDH infants.

Conclusions: Our prenatal risk stratification system, which demonstrated a significant difference in postnatal status and final outcome, would allow for accurate estimation of the severity of disease in fetuses with isolated CDH, although it needs prospective validation in a different population.

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Congenital diaphragmatic hernia (CDH) remains one of the most challenging anomalies facing pediatric surgeons and neonatologists, as it has a broad spectrum of severities dependent on components of pulmonary hypertension and hypoplasia of the lungs. An accurate prenatal severity assessment is essential for standardization of prenatal and postnatal care for individual cases because severity directly affects mortality and morbidity. Prenatal prognostic classification of CDH would provide the family with more precise information about the course of treatment and allow a management protocol based on risk to be established. This may minimize excessive treatment and medical expenses for low-risk patients while maximizing effective management in high-risk patients.

Several prenatal prognostic parameters for fetal CDH have previously been proposed by other investigators [1-14]. It has been validated by multiple centers that the presence of liver herniation is among the most reliable predictors of severity and mortality in CDH [1-6]. Stomach position was also studied as a prognostic indicator along with liver herniation [8-10]. Moreover, estimation of fetal lung size or evaluation of fetal lung characteristics has reportedly been used for severity prediction [11-18]. Among these fetal lung assessments, the lung area–to–head circumference ratio (LHR) is the most commonly used as a prenatal prognostic factor [8,11,18]. However, LHR is no longer considered to be independently predictive of survival by several investigators [2,19-21] because it has been shown to increase according to gestational age [15,16,22,23]. The observed to expected LHR has been proposed to provide a constant value throughout the gestational period [22], but in that study, this value was standardized by the normal lung size value of each population corresponding to gestational age without taking individual fetal growth into consideration.

In contrast, the contralateral lung–to–thorax transverse area ratio (L/T ratio) appears to be a reliable predictive parameter in fetal CDH, as it was originally reported to be constant throughout the gestational period in normal fetuses [12], and is reportedly not strongly influenced by gestational age even in fetuses with CDH [15,16]. Although combining several reliable prognostic parameters including the L/T ratio may contribute to the establishment of a prenatal risk stratification system for fetal CDH, such approaches have not been successful to date. The aim of this study was to establish a prenatal prognostic classification system for risk-stratified management of fetuses with isolated CDH based on a combination of fetal ultrasonographic findings including liver position and L/T ratio.

1. Materials and methods

1.1. Patient selection and data collection

We conducted a multicenter retrospective review of the medical records of 117 fetuses with isolated CDH, diagnosed prenatally, born at 5 participating centers during the period between January 2002 and December 2007 [10,24]. Patients with serious associated anomalies such as major cardiac malformations and chromosomal abnormalities were excluded. Two cases with bilateral diaphragmatic hernia and 12 without L/T ratio measurements were excluded from the analysis. All 103 eligible patients were managed by maternal transport, with immediate resuscitation followed by neonatal intensive care mostly with high-frequency oscillatory ventilation. In all institutions, the blood gas parameter goals were $PaCO_2 < 60$ to 70 mm Hg and preductal $SpO_2 > 90\%$, under the concept of permissive hypercapnia [25] and permissive hypoxia. All institutions had extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO) capability, which were initiated according to the clinical decisions of each institution; indication criteria were not defined prospectively. Diaphragmatic repair was performed when respiratory and circulatory functions had stabilized. As the criteria of preoperative stabilization were not defined prospectively, operability of each patient was determined according to the clinical decisions of each institution. This study was approved by the institutional review boards of all 5 participating centers.

The primary outcome measure was mortality at 90 days. Prenatal ultrasonographic findings including polyhydramnios, fetal liver position, fetal stomach position, and the L/T ratio were collected at 3 times, according to gestational age at diagnosis: the earliest determination before 30 weeks of gestation, between 30 and 35 weeks of gestation, and after 35 weeks of gestation. Polyhydramnios was regarded as positive if the maximal vertical pocket was more than 8 cm. Only those patients with obvious liver herniation (ie, whose liver occupied more than one third of the thoracic space) were regarded as liver-up. Those with slight liver herniation or with liver herniation first recognized during surgery were regarded as liver-down. Fetal stomach position was categorized as contralateral stomach herniation, defined as more than half of the stomach having herniated into the contralateral thoracic cavity (equivalent to grade 3 in our previous report [10]) or others. The L/T ratio was measured at the transverse section containing the 4-chamber view of the heart by ultrasonography [12]. Briefly, the L/T ratio was defined as the area of the contralateral lung, which was determined by tracing around the contralateral lung, divided by the area of the thorax surrounded by the inner border of the bilateral ribs, the sternum, and the vertebra [15]. The cutoff value of the L/T ratio was set at 0.08 based on our previous studies [15,16,26]. Polyhydramnios, liver-up, and contralateral stomach herniation were categorized as positive if 1 of the 3 determinations was positive. The L/T ratio value was represented by the minimal value of 3 determinations, as in our previous report [16].

Postnatal factors, including sex, gestational age at birth, birth weight, mode of delivery, hernia side, Apgar scores at 1 and 5 minutes, preductal arterial blood gas data within

24 hours after birth, use of circulatory support (ECMO, prostaglandin I_2 administration, prostaglandin E_1 administration, iNO), ductus arteriosus (DA) shunt direction within 24 hours after birth, size of diaphragmatic defect judged intraoperatively, need for patch closure, duration of respiratory support (iNO, mechanical ventilation, oxygen administration), duration of hospitalization, 90-day survival, survival to discharge, intact discharge, and survival time, were collected as secondary measures. Intact discharge was defined as being discharged from the hospital with no need for home treatments such as ventilatory support, oxygen administration, tube feeding, and/or parenteral nutrition.

1.2. Analysis of prenatal factors and formulation of the prenatal risk stratification system

Odds ratios (OR) of prenatal parameters for mortality at 90 days were compared by univariate and multivariate analyses. According to the magnitude of the OR, patients were first stratified by the most powerful factor, and then each stratified group was subsequently divided into 2 subgroups by the second most powerful factor. The risk stratification system was formulated based on the results of the mortality at 90 days in each subgroup. Patient demographics and prenatal and postnatal profiles including parameters indicating the respiratory status, circulatory status, surgical findings, and outcome were compared among the groups classified using this approach.

1.3. Statistical analysis

Univariate analyses were performed to assess the magnitude of risks associated with prenatal variables for mortality at 90 days using the χ^2 test and Fisher exact test. Multiple logistic regression analysis was also performed to estimate the ORs for prenatal variables adjusted for confounding. The stepwise selection method (P value criteria <.20) was used to select variables correlating with the mortality at 90 days. Crude ORs and adjusted ORs with 95% confidence intervals (CI) were calculated. The mean and SD were used to describe continuous variables. The median and interquartile range were used to describe ordinal scales or durations of treatment in the cases with censoring. The frequency and percentages were used to describe categorical data. One-way ANOVA with Tukey post hoc honestly significant difference test was used for comparison of continuous variables. The Kruskal-Wallis test was used for comparison of Apgar scores. The χ^2 test and Fisher exact test were used for analysis of categorical data. The log-rank test and Kaplan-Meier method were used to compare the treatment durations and survival times. P values lower than .05 were considered statistically significant. Statistical analyses were performed with JMP (version 8.02; SAS Institute, Cary, NC).

2. Results

2.1. Analysis of prenatal factors and formulation of the prenatal risk stratification system

Crude ORs for the factors significantly associated with mortality at 90 days were 18.6 for liver-up, 13.6 for L/T ratio <0.08, and 11.0 for contralateral stomach herniation. Adjusted ORs for liver-up and L/T ratio <0.08 were statistically significant, whereas that for contralateral stomach herniation did not reach statistical significance (Table 1). The mortality at 90 days of 4 subgroups, first stratified by the most powerful factor (liver herniation) and subsequently by the second most powerful factor (L/T ratio), are shown in Figure 1 (Fig. 1). The mortality at 90 days of all cases was 19.4%, whereas that of fetuses with liver-down and L/T ratio ≥0.08 was 0.0%. We thus defined the latter as group A (low-risk group). Fetuses with liver-down and L/T ratio <0.08 and those with liver-up and L/T ratio ≥0.08 were combined into group B (intermediate-risk group), since they had the same mortality at 90 days of 20.0%. The mortality at 90 days of fetuses with liver-up and L/T ratio <0.08 was 65.0%, and these constituted group C (high-risk group). The numbers of patients in groups A, B, and C were 48, 35, and 20, respectively (Fig. 1).

Table 1 Univariate and multivariate analyses for mortality at 90 days

Variable	n (%)	OR for mortality at 90 d (95% CI)	P
Univariate analysis		Crude OR	
Liver-up (ref: liver-down)	45 (43.7)	18.6 (4.04-86.3)	<.001
L/T ratio <0.08 (ref: ≥0.08)	30 (29.1)	13.6 (4.28-43.2)	<.001
Contralateral stomach herniation (ref: others)	25 (24.3)	11.0 (3.64-33.1)	<.001
Polyhydramnios (ref: no polyhydramnios)	31 (30.1)	2.27 (0.83-6.21)	.114
Multiple logistic regression analysis		Adjusted OR	
Liver-up (ref: liver-down)	45 (43.7)	9.34 (1.92-70.2)	.011
L/T ratio <0.08 (ref: ≥0.08)	30 (29.1)	8.28 (2.33-33.3)	.002
Contralateral stomach herniation (ref: others)	25 (24.3)	2.61 (0.64-10.5)	.173

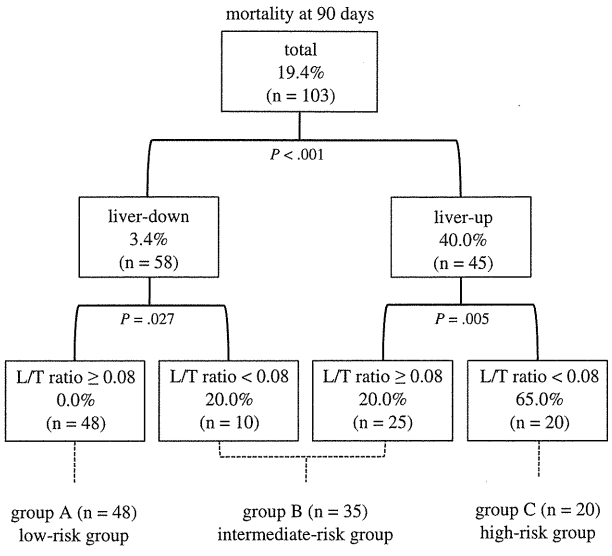

Fig. 1 Mortality at 90 days of subgroups stratified by liver position and L/T ratio. Group A includes patients with liver-down and L/T ratio ≥0.08; group B patients with liver-down and L/T ratio <0.08 or liver-up and L/T ratio ≥0.08; group C patients with liver-up and L/T ratio <0.08.

2.2. Comparison of CDH severity in each prenatal risk group

There were no significant differences in patient demographics, including sex, gestational age at diagnosis, gestational age at birth, and birth weight, among the 3 groups. The only exception was mode of delivery. Groups B and C had higher rate of cesarian sections, which were performed according to the clinical decisions of each institution, as the criteria of cesarian sections were not defined prospectively. Although the incidences of polyhydramnios did not differ significantly, not surprisingly, there were significant differences in liver-up and the L/T ratio as well as stomach herniation based on how the stratification system was formulated (Table 2). Apgar scores and preductal arterial blood gas data were significantly worse in group C. There were also significant differences in the duration of respiratory support such as iNO, artificial ventilation, and O_2 administration. Consequently, there were significant differences in the duration of hospitalization among the 3 groups (Table 3). DA shunt directions evaluated within 24 hours after birth, which suggest the severity of pulmonary hypertension, differed significantly among the 3 groups. The number of the patients who used circulatory support such as ECMO, prostaglandin I_2 administration, prostaglandin E_1 administration, and iNO were 14, 23, 35, and 86, respectively. There were significant differences in the use of such circulatory support to manage pulmonary hypertension among the 3 groups (Table 4). Although diaphragmatic repair could be performed in all group A patients, surgery was not possible in 4 group B patients (11.4%) and in 7 group C patients (35%) due to their unstable conditions. There were also significant differences in the proportions of patients with diaphragmatic defects exceeding 75%, as judged intraoperatively. Among the 13 group C patients undergoing surgery, 12 (92.3%) required patch closure, whereas only 10 (20.8%) required patch closure in group A (Table 5). There were significant differences in morbidity and mortality among the 3 groups. The rate of survival to discharge was 100.0% and the intact discharge rate was 95.8% in group A, whereas the corresponding rates were 74.3% and 60.0% in group B, and 20.0% and 5.0% in group C (Table 5). There were also statistically significant differences in survival curves among the 3 groups (Fig. 2).

3. Discussion

An accurate prenatal severity assessment for individual fetuses with CDH is essential for standardization of prenatal and postnatal treatments, since CDH has a broad spectrum of severities that directly affects the mortality and morbidity for the patients. We endeavored to establish such a risk stratification system by applying a combination of several reliable prognostic parameters previously proposed for use in fetuses with CDH [1-18]. These prognostic parameters are

Table 2 Demographics and prenatal findings of fetuses with CDH

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	*P*
Sex (male/female)	23/25	23/12	12/8	.254
Side of hernia (right/left)	0/48	2/33	2/18	.119
Gestational age at diagnosis (wk), mean ± SD	29.6 ± 5.9	27.5 ± 5.2	28.3 ± 5.5	.231
Gestational age at birth (d), mean ± SD	266 ± 14.3	266 ± 12.4	266 ± 10.2	.995
Birth weight (kg), mean ± SD	2.82 ± 0.50	2.74 ± 0.51	2.61 ± 0.59	.302
Caesarian section (%)	23.8	60.0	75.0	.001
Polyhydramnios (%)	20.8	40.0	35.0	.148
Liver-up (%)	0.0	71.4	100.0	<.001
Stomach herniation (%)	4.2	25.7	70.0	<.001
L/T ratio, mean ± SD	0.121 ± 0.032*	0.099 ± 0.028†	0. 058 ± 0.016‡	<.001

* $P < .05$, A versus B; † $P < .05$ B, versus C; ‡ $P < .05$, C versus A.

Table 3 Respiratory status and respiratory support in CDH patients

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	*P*
Apgar 1 min, median (interquartile range)	5 (3-7) (n = 48)	3.5 (2-6) (n = 34)	3 (2-4) (n = 19)	.002
Apgar 5 min, median (interquartile range)	6 (4.25-7.75) (n = 48)	5 (3.5-8) (n = 33)	3.5 (2-5.25) (n = 18)	.006
Highest pre-Pao_2 (mm Hg), mean ± SD**	284 ± 122* (n = 44)	211 ± 132 (n = 25)	129 ± 117‡ (n = 18)	<.001
Lowest pre-$Paco_2$ (mm Hg), mean ± SD**	33.4 ± 11.2 (n = 42)	36.8 ± 16.3† (n = 29)	49.8 ± 26.0‡ (n = 19)	.002
Duration of iNO (d), median (interquartile range)	8 (5-12)	11 (7-19)†	34 (22-40)‡	<.001
Duration of ventilation (d), median (interquartile range)	14 (9-28)*	30 (21-48)†	545 (30-747)‡	<.001
Duration of O_2 administration (d), median (interquartile range)	23 (15-38)*	43 (37-73)†	555 (529-748)‡	<.001
Duration of hospitalization (d), median (interquartile range)	48 (39-69)*	73 (56-108)	162 (95-545)‡	<.001

* $P < .05$, A versus B; †$P < .05$, B versus C; ‡$P < .05$, C versus A.
** Highest pre-Pao_2 and lowest pre-$Paco_2$ were measured within 24 hours after birth.

divided broadly into 2 categories. One is the indirect factor of pulmonary hypoplasia, which is an estimation of how much viscera (ie, liver herniation and stomach position) compresses the fetal lungs. The other is the direct parameter of fetal lung development itself. The magnitudes of ORs in univariate and multivariate analyses for mortality at 90 days were compared, and 2 powerful prenatal factors were eventually identified in each category.

The fetal liver position was the most powerful prognostic factor judging from OR magnitude. It has already been reported by many investigators that fetal liver herniation is the most reliable predictor of the severity and mortality in fetuses with CDH [1-6]. Although stomach position was also a good prognostic indicator, along with liver herniation [8-10], we selected fetal liver herniation based on the OR being larger than that for stomach herniation. Furthermore, these 2 predictors seemed to be mutually confounding factors. There is marked variation in the definition of liver herniation, and the "liver-up" concept differs markedly among authors [5,7]. In the present study, we defined liver-up as liver herniation in which the liver occupied more than one third of the thoracic cavity [10] based on previous studies [4,6], because there is a possibility of overestimating the affect of lung compression if situations such as slight liver herniation and liver herniation first recognized during surgery are included among the "liver-up" cases. Liver herniation occupying one third of the thoracic cavity turns out to be a good cutoff value for prediction, as liver-up defined by this means demonstrated a satisfactory OR.

The L/T ratio was the second most powerful prognostic parameter in our analysis. Many factors, such as lung area [11,12,16,18], volume [4,13,14], and signal intensity on magnetic resonance imaging [17], as well as pulmonary artery blood flow [27], have previously been proposed as means of estimating fetal lung development. Among these parameters, the simplest approach is to determine the fetal lung area using 2-dimensional ultrasonography, as is now widely done in multiple centers. LHR [8,11,18] has long been the most commonly used parameter for evaluating the fetal lung area. However, LHR was shown to increase according to gestational age [15,16,22,23]. Therefore, LHR is no longer considered to be independently predictive of survival by several investigators [2,19-21]. In contrast, we have previously demonstrated that the L/T ratio, which is not markedly influenced by gestational age even in fetuses with CDH [15,26]. We studied in detail to compare the reliability of L/T ratio and LHR in the same database and found that the L/T ratio is more reliable than the LHR [16]. Moreover, a manual tracing of the lung borders, which is conducted to obtain the L/T ratio, is reportedly a more reproducible measurement than the multiplication of the lung diameters, which is used for LHR determination [23,28]. The observed to expected LHR was proposed to provide a constant value throughout the gestational period, and it showed excellent receiver operating characteristic curve performance [22]. However, determining the observed to expected LHR requires the expected LHR in normal fetuses to be used for standardization of each relevant patient population, and the

Table 4 Circulatory status and circulatory support in CDH patients

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	*P*
Left to right dominant shunt at DA (%)*	39.1 (n = 46)	36.4 (n = 33)	0.0 (n = 18)	.007
Right to left dominant shunt at DA (%)*	37.0 (n = 46)	51.5 (n = 33)	72.2 (n = 18)	.036
Use of ECMO (%)	2.1	14.3	40.0	<.001
Use of prostaglandin I_2 (%)	8.3	28.6	45.0	.002
Use of prostaglandin E_1 (%)	14.6	40.0	70.0	<.001
Use of iNO (%)	70.8	94.3	95.0	.005

* Shunt direction at the DA was evaluated within 24 hours after birth.

Table 5 Operative findings, morbidity, and mortality

	Group A (n = 48)	Group B (n = 35)	Group C (n = 20)	*P*
Inoperable cases (%)	0.0	11.4	35.0	<.001
Diaphragmatic defects exceeding 75% (%)	17.8 (n = 45)*	81.5 (n = 27)*	100.0 (n = 11)*	<.001
Need for patch closure (%)	20.8 (n = 48)	71.0 (n = 31)	92.3 (n = 13)	<.001
90-d Survival (%)	100.0	80.0	35.0	<.001
Survival to discharge (%)	100.0	74.3	20.0	<.001
Intact discharge (%)	95.8	60.0	5.0	<.001

* The size of diaphragmatic defect was not determined in several cases due to lack of intraoperative information.

availability is relatively low for some populations. Furthermore, there appears to be a problem in that individual fetal growth variation is not considered when determining the observed to expected LHR, relying instead on a standardized mean value from fetuses showing normal growth [22].

In the present study, ECMO and iNO were performed in 14 (13.6%) and 86 (83.5%) patients, respectively. As compared with previous reports [3,13,29-31], our results demonstrated less frequent use of ECMO and high use of iNO. In recent years, there has been an obvious trend in institutions in Japan to use ECMO less frequently with an associate increase in the use of iNO and prostaglandin E_1 administration for pulmonary hypertension [32-34], as was described by the CDH study group [35]. We usually use iNO without hesitation, if there is only a slight difference between the preductal and postductal oxygen saturation or blood gas data to reduce pulmonary artery resistance, with the ultimate goal of preventing right ventricular failure by removing the afterload on the right ventricle [32,33]. At present, in the 5 participating institutions, ECMO is being applied only for the most severe respiratory insufficiency cases. However, some infants with extremely severe pulmonary hypoplasia have been considered not to be indicated even for ECMO. This may account for the high mortality rate (64.3%) of our ECMO cases and the high inoperable rate (9.0%) of our non-ECMO cases.

One major limitation of this study is that the liver positions and L/T ratios were determined by various investigators at each participating institution, rather than by a small number of sonologists or other experienced judges, as would have been ideal to assure consistency. There may be some variation in the accuracy of the measurements in the present study and a prospective study in which the parameters determined by limited number of investigators may be needed to verify the accuracy of this risk stratification system. The other limitation of this study is that the risk group could not be confirmed until the end of gestation. In the present study, the presence of liver-up and an L/T ratio <0.08 were judged based on the worst value among the 3 representative measurements conducted before 30 weeks of gestation, between 30 and 35 weeks of gestation, and after 35 weeks of gestation. Because this process was applied for all of our determinations, the cases finally classified into the high-risk group were not always graded as being in this group from the beginning. Therefore, this system may not be useful for determining the need for maternal transport to a center offering fetal intervention [36]. Severity must be evaluated as early as possible, ideally before 28 weeks of gestation, to optimize the effects of early fetal intervention.

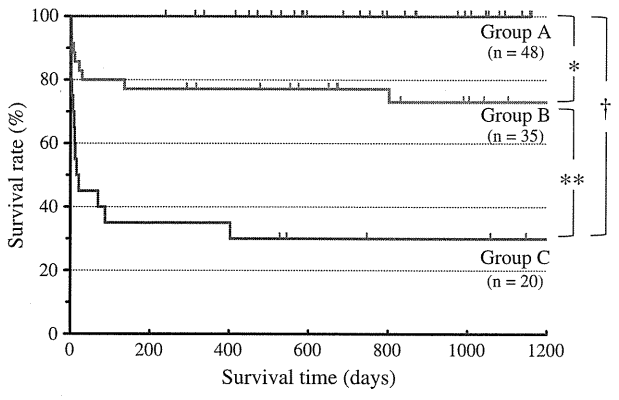

Fig. 2 Survival curves for patients with isolated CDH, compared using the prenatal risk stratification system. * $P < .001$; † $P < .001$; ‡ $P < .001$.

We have previously endeavored to devise a simple classification system based only on indirect factors reflecting how much the viscera compress the fetal lungs (ie, liver and stomach position) by applying a uniform multicenter survey [10]. This simple classification system has a clear advantage for screening candidates for fetal intervention, since the risk group can be determined by the findings of the earliest fetal evaluation. Compared with the previous simple classification system, the new risk stratification system was found to be more reliable in terms of accuracy and the ability to clearly separate the mortality and morbidity of the CDH patients, which suggests that it has an advantage for risk-stratified management after birth.

The incidence of right-sided CDH was relatively low in our cohort [24] compared with the previous reports [35,37]. The reason for this shift was unclear. However, the incidence did not seem to be markedly influenced by selective termination of pregnancy for fetuses with right-sided CDH, as only 13 (12.6%) cases had been diagnosed before 22 weeks of gestation, when the termination of pregnancy is legally accepted in our country [38]. We sought to treat right-sided CDH together with left-sided CDH in this study. Even though the incidence of liver-up and the original contralateral

lung area may differ between right- and left-sided CDH due to anatomical reasons, we considered it to be more practical to apply the same stratification to both sides in fetuses with CDH. All 4 cases with right-sided CDH were classified into the intermediate- or high-risk group according to their L/T ratios. Consequently, the results are therefore considered to be consistent with those of previous studies [8,39].

Our prenatal risk stratification system, which demonstrated a significant difference in postnatal status and final outcome, may allow for accurate estimation of the severity of disease in fetuses with isolated CDH such that management protocols could be established according to risk. This would minimize excessive treatment and medical expenses for low-risk patients and maximize effective management in high-risk patients. As the present study was a retrospective analysis, a prospective study in a different population will therefore be needed to verify the accuracy and the universal applicability of this risk stratification system.

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ORIGINAL ARTICLE

Use of the medical information on the internet by pregnant patients with a prenatal diagnosis of neonatal disease requiring surgery

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Abstract
Purpose The purpose of this study was to clarify the current status and the problems associated with using medical information on the internet during pregnancy in patients prenatally diagnosed with fetal abnormalities at a single Japanese institution.
Methods A written, anonymous questionnaire survey was conducted in 155 pregnant patients who had been prenatally diagnosed as having neonatal surgical diseases between January 2000 and December 2009, and their families.
Results Forty-three out of the 75 responding families (57.3%) had used medical information available on the internet during their pregnancy. The availability of information, assessed during 2 year-increments, has increased rapidly in the past 4 years. When the explanation of a physician was compared with the information provided by the internet, the knowledge or impression of the disease was different in 60% of cases and similar in 33% of cases. More importantly, 60% of the patients felt that the information obtained from the internet was more pessimistic than the physician's explanation.
Conclusion The number of pregnant patients who have used medical information on the internet has rapidly increased in the recent years. Subjects who used this information were more likely to experience a sense of anxiety and feelings regarding the seriousness of the disease.

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Keywords Internet · Prenatal diagnosis · Questionnaire survey · Medical information · Neonatal surgery

Introduction

Recently, the patients' use of medical information available on the internet has been spreading rapidly in our country, as well as all over the world. However, careful consideration is necessary for the use of such information, as there are many problems, such as ensuring the reliability of the information, protection of personal information, and the neutrality of the website. When we provide the patients information about a prenatal diagnosis, we occasionally receive questions from pregnant patients and their families based on information obtained from the internet.

Pregnant patients with a prenatal diagnosis of fetal abnormalities may become anxious due to the lack of information. Thus, they may have a tendency to depend on the medical information found in the internet [1, 2], which can affect their feelings and decisions. However, it is not clear how much such patients and their families depend on this medical information, and what kind of problems are caused by this behavior. The purpose of this study was to clarify the current status and the problems associated with the use of medical information available on the internet during pregnancy by patients diagnosed as having a fetus with neonatal surgical diseases.

Patients and methods

A written, anonymous questionnaire survey was conducted in 155 women, including seven who lost a child, whose present addresses were available, who had been prenatally