		臼井班
1，診療ガイドラインがカバーする内容に関する事項		
1　タイトル		頚部・胸部リンパ管疾患診療ガイドライン
2　目的		呼吸障害を生ずる可能性のある頚部・胸部のリンパ管疾患に対する診療のガイドラインを作成する。
3　トピック		頚部・胸部リンパ管奇形（リンパ管腫）・リンパ管腫症・乳び胸水、呼吸障害
4　想定される利用者、利用施設		☆一般：患者、患者家族、医療従事者、その他 ☆診療科：小児外科、小児科、産婦人科（胎児診断、婦人科）、耳鼻咽喉科、形成外科、口腔外科、胸部外科、一般・消化器外科、放射線診断科、病理診断科等 ☆施設：大学病院、小児病院、周産期・小児センターなど
5　既存ガイドラインとの関係		国外では系統的に作成されたガイドラインは存在しない。本邦では、従来「リンパ管腫」といわれていた疾患は、平成24年に本邦において発行された「血管腫・血管奇形ガイドライン」において「リンパ管奇形」として一部分に示された。 「リンパ管奇形」は国際潮流となりつつあるISSVA分類に則った疾患名であり、混乱を避けるため、今後国内でのコンセンサスを得て統一されることが望ましい。現時点では「リンパ管奇形（リンパ管腫）と併記する。 「血管腫・血管奇形ガイドライン第1版」では、頚部・胸部に限らず硬化療法に関するクリニカルクエスチョンとそれに対する推奨が示された。このたび呼吸障害を生ずる小児の頚部・胸部の難治性疾患の一つとしてリンパ管腫およびリンパ管関連疾患についてガイドラインを作成するに至ったのは、生命予後に関わる重大な疾患の一つとして、リンパ管関連疾患をまとめてとらえることが必要であったからである。 「血管腫・血管奇形ガイドライン」が全身の体表・軟部を対象としているのに対して、より絞られた領域を対象としているが、内容的にはほとんど重ならないため、お互いに補填するような意義を持つ。また同様に、現在頚部・胸部とは別に「腹部リンパ管疾患診療ガイドライン」を同時に作成しつつある。最終的にはリンパ管奇形(リンパ管腫）の部門を統合する。
6　重要臨床課題	重要臨床課題1	リンパ管腫の中でも気道狭窄を生じる部位にあるものは、生命に危険を及ぼすものである。縦隔内にて物理的に気管や気管支を圧迫し気道狭窄をきたしたり、縦隔が大きく張り出して胸郭内を占めるため胸腔が狭くなるなどして、呼吸障害を生ずる。 このような場合には積極的かつ有効な治療が必要とされるが、縦隔内の病変は周囲の心大血管や横隔神経、胸管などの重要臓器との関係から慎重に治療法が選択されねばない。しかしながら臨床の場においては実際には判断に難渋することが多い。 外科的切除、硬化療法等の治療につき、合併症リスク、予後等を含めて現在の知見を統合することが望まれる。
	重要臨床課題2	頚部リンパ管腫は露出部にあることより整容性の問題が大きいが、重症例では特に気道狭窄の問題が重要となる。 治療の柱の一つである硬化療法は嚢胞性の症例に対しては概ね有効であるが、治療後には患部の腫脹が見込まれるため、新生児期には気道狭窄症状出現や増悪が懸念される。上気道は新生児期から成長するに従い、脆弱性は改善し物理的に広くなるため気道狭窄症状を起こしにくくなる傾向を認めるため、乳児期に気道狭窄症状を呈さない症例に対してどのように治療を進めるかについては、判断に苦慮することがある。 この問題について指針の作成を試みる。
	重要臨床課題3	舌はリンパ管奇形（リンパ管腫）の発生する部位のひとつであるが、舌だけにとどまらず頚部に広汎に分布することも多い。舌はこれ自体の腫脹により突出や出血などによる整容性の問題を生じるが、容易に口咽頭腔を占拠し、閉口障害、発語困難、呼吸障害や経口摂取障害を生じうる。治療に際しては形成外科、口腔外科、耳鼻咽喉科、小児外科など様々な診療科が担当している。 治療の選択においては舌内の病変の分布、他の部位への広がりや嚢胞成分の程度、血管分布などの個々の患者臨床情報に加えて、硬化療法の有効性、切除術の有効性、またそれぞれの治療法における合併症や再発のリスクなどの一般情報を加えて総合的に考える必要がある。 その中で特に舌部分切除による減量手術の有効性につき検討する。

	重要臨床課題4	新生児期に認められる原発性の乳び胸水は難治性であることが多く、救命できないこともある。胸水貯留による呼吸不全に対しては胸腔ドレナージがおこなわれるが、その後乳び胸水の軽快まで新生児科医を中心として栄養療法、ステロイド、オクトレオチド療法などの保存的療法が行われる。 しかしこれらの治療で軽快しない難治例に対しては胸管結紮、胸膜癒着術等の物理的な外科的介入が行われることもあるが、その効果については十分なコンセンサスが得られてはいない。どのタイミングで外科的介入をおこなうべきか、またこの病態に対して積極的な外科的介入は本当に有効なのかどうかなどの臨床的疑問に対する指針が求められている。
	重要臨床課題5	全身に多彩な症状を起こす難治性疾患であるリンパ管腫症・ゴーハム病は胸部に病変が存在する場合に特に致死率が高いことが平成25年度までに行われた厚労省小関班研究にて明らかとなった。 胸部病変としては難治性の乳び胸水、心嚢液貯留、肺実質のリンパ鬱滞、胸膜肥厚、肋骨をはじめとする胸部の骨溶解などを主に認める。治療を要する病態である乳び胸水・心嚢液はしばしば難治性であり、時に致死的となる。コンセンサスの得られた有効な治療法は現在知られていないが、治療の成功例についてはデータが蓄積されている。現時点ではこの難治性の疾患に対して得られる有効な治療法は何であるのかは回答の求められている最も大きな課題である。
	重要臨床課題6	
	重要臨床課題7	
	重要臨床課題8	
7 ガイドラインがカバーする範囲		小児に発生し上下気道に影響を及ぼし呼吸障害を生じうるリンパ管疾患 具体的には頚部・胸部の気道周囲のリンパ管奇形(リンパ管腫)、リンパ管腫症・ゴーハム病、また新生児の乳び胸水を対象として、これらに対する長期的臨床的問題、治療、合併症についての重要な課題について検討する。
8 CQリスト	CQ1	CQ1:縦隔内で気道狭窄を生じているリンパ管奇形(リンパ管腫)に対して効果的な治療法は何か？
	CQ2	CQ2:頚部の気道周囲に分布するリンパ管奇形(リンパ管腫)に対して、乳児期から硬化療法を行うべきか？
	CQ3	CQ3:舌のリンパ管奇形(リンパ管腫)に対して外科的切除は有効か？
	CQ4	CQ4:新生児期の乳び胸水に対して積極的な外科的介入は有効か？
	CQ5	CQ5:難治性の乳び胸水や心嚢液貯留，呼吸障害を呈するリンパ管腫症やゴーハム病に対して有効な治療法は何か？
	CQ6	
	CQ7	
	CQ8	
	CQ9	
2，システマティックフェビューに関する事項		
1 実施スケジュール		開始:平成26年12月 一次スクリーニング:平成26年12月末まで 二次スクリーニング:平成27年2月末まで まとめ:平成27年3月末まで
2 エビデンスの検索	利用するエビデンスのタイプ	・コクランライブラリー・システマティックレビュー(SR)/メタアナリシス(MA)論文、個別研究論文、症例報告、エキスパートオピニオンをこの優先順位で検索する。優先順位の高いエビデンスタイプで十分なエビデンスが見いだされた場合は、そこで検索を終了して、エビデンスの評価と統合に進む。ただし該当する疾患領域ではエビデンスレベルの高い文献は非常に少ないと予想される。 ・個別研究論文としては、ランダム化比較試験(RCT)、非ランダム化試験(CCT)、観察研究を検索の対象とする。偶発症など症例報告の検索が必要なものについては、ケースシリーズ、症例報告まで検索対象とする。

	利用するデータベース	・SR/MAについては、英文はCochrane ReviewとPub Med、和文は医中誌とする ・個別研究については、英文はPub Med、和文は医中誌とする ・既存の診療ガイドラインについては、英文はGuideline International NetworkのInternational Guideline Library、和文は日本医療機能評価機構EBM普及推進事業(Minds)とする
	文献検索の期間	1990～2014年9月末
3 文献の選択基準、除外基準	選択基準	RCTやMA、SR論文が存在すれば採用する。 1例報告も除外しない。
	除外基準	会議録や本文のない文献は除外する。
4 エビデンスの評価と統合の方法		Minds診療ガイドライン作成の手引き2014に基づき、エビデンス総体の評価と統合を行う。ただし、適当なPICOを設定できないCQについては、キーワードを元に検索した文献を総合的に勘案してエビデンスを評価する。
3，推奨作成から最終化、公開までに関する事項		
1 推奨作成の基本方針		☆ Minds診療ガイドライン作成の手引き2014年則って作成する。 ☆ 文献検索を行ってもエビデンスレベルの高い文献はほとんど無いと予想されている。システマティックレビューでは実際に検索を行い、それを確認する。その上で、研究班メンバーを中心としたエキスパート・オピニオンにより推奨文及び解説文を作成し、研究班の作成グループの審議により決定する。意見の一致をみない場合には、投票を行って決定する。 ☆ 推奨の決定には、エビデンスの評価と統合で求められた「エビデンスの強さ」、「益と害のバランス」の他、「症例の多様性」、「患者の価値観の多様性」にも考慮して、推奨とその強さを決定する。
2 最終化		
3 外部評価の具体的方法		☆推奨・ガイドライン形式の妥当性について、Minds担当者に評価を受ける。 ☆日本小児外科学会、日本形成外科学会、日本IVR学会のガイドライン担当部門に科学的妥当性や推奨の適応・実現可能性等につき評価を受ける。 AGREEIIIに則り作成方法の評価を行う 公開後もリンパ管疾患情報ステーション等で常に評価を受ける
4 公開の予定		Mindsのサイト、リンパ管疾患情報ステーション、冊子

資料5-3

1	気道狭窄症状の既往	なし	あり											
2	狭窄症状の種類	なし	あり											
3	全経過における気管切開の既往	なし	あり											
4	気切日													
5	閉鎖の有無	閉鎖した	閉鎖していない											
6	閉鎖日													
8	出生時外観上の腫瘤の有無	あり	なし											
9	気管切開の直接の原因は何か	急性腫脹	治療前の予防的気切	出生直後からの気道閉塞	その他(自由記載)									
9a	急性腫脹の原因	出血	感染	出血と感染	硬化療法	外科的切除	感冒	その他(自由記載)						
10	病変と気道との関係	離れている	接している											
11	気道と接触している範囲	舌	咽頭部(声門上)	喉頭部(声門上)	喉頭部(声門下)	気管(頸部)	気管(縦隔内)							
12	接している部位毎の接触範囲	接触範囲≦1/4周	1/4<接触範囲≦1/2周	1/2<接触範囲≦3/4	3/4<接触範囲<全周	全周								
13	気道狭窄の直接の原因となっている部位	声門上	声門	声門下顎部	縦隔内	不明								
14	閉塞を来す病変に対して行った治療	なし	硬化療法	外科的切除	内科的療法	放射線療法	レーザー	その他(自由記載)						
15	治療により気道狭窄症状は改善したか	増悪	不変	改善したがまだ残る	症状消失									
16	治療により気道に接する病変範囲は軽減したか	不変	部分的に改善	消失										
17	気道に接する部位の病変のタイプは嚢胞性か海綿状か	嚢胞性	海綿状	混合	不明									
18	縦隔病変への治療の有無	なし	あり											
18a	治療(開始)時期	胎児期	新生児期	乳児期(1歳未満)	幼児期(1歳以上6歳未満)	学童期(6歳以上15歳未満)	成人期(16歳以上)							
19	発見時症状	なし(胸部異常陰影)	なし(胸部異常陰影以外(　))	浮腫・水腫	呼吸困難	咳・喀痰	喘鳴	発熱	動悸	嚥下困難・障害	痛み・圧迫感	ショック	胸水	その他(　)
20	治療時症状	なし(胸部異常陰影)	なし(胸部異常陰影以外(　))	浮腫・水腫	呼吸困難	咳・喀痰	喘鳴	発熱	動悸	嚥下困難・障害	痛み・圧迫感	ショック	胸水	その他(　)
21	治療時縦隔内病変部位	縦隔(特定できず)	上縦隔	前縦隔	後縦隔	その他(　)								
22	治療方法	全摘除	部分摘除	硬化療法(使用薬剤(　))	嚢胞穿刺	ドレナージ	その他(　)							
22a	切除の場合のアプローチ法	摘出術(胸骨正中切開による)	摘出術(右開胸による)	摘出術(左開胸による)	摘出術(鏡視下による)	その他(　)								
23	治療後合併症	乳び胸	出血	横隔神経麻痺	反回神経麻痺	縦隔炎	その他(　)							
24	治療後病変の有無	病変なし	病変残存あり	病変消失後再発あり	不明									
25	治療後症状の有無													
26	日常生活上の不自由	なし	軽度	中等度	重度									

告示番号 14 慢性呼吸器疾患　平成（　　）年度 小児慢性特定疾病　医療意見書

受給者番号（　　）	新規登録 ・ 継続 ・ 転入（転出地：　　）				
患者	ふりがな 氏名	男 ・ 女	生年月日	平成　年　月　日（満　歳）	
出生都道府県※1		出生体重	g	出生週数	在胎　週
現在の身長※2	.　cm	現在の体重※2	.　kg	母の生年月日	昭和 平成　年　月　日
発病	年　月 頃	初診日	年　月　日		
大分類病名	12 リンパ管腫／リンパ管腫症	細分類病名	13 リンパ管腫／リンパ管腫症		

※1 出生都道府県は母子健康手帳に記載されている出生した際に出生届を提出した住民票の所在地を記入
※2 現在の身長・現在の体重は小数点1位まで記入

1.臨床所見

現在の症状

該当するものに○をつけ、必要な場合には（ ）内に記載

罹患部位（複数選択可）

頸部　（ なし ・ あり → 左 ・ 右 ・ 両側 ）
頬部　（ なし ・ あり → 左 ・ 右 ）
舌　（ なし ・ あり ）
下縦隔　（ なし ・ あり ）
腋窩　（ なし ・ あり → 左 ・ 右 ）
その他の部位　（ なし ・ あり → 詳細：　　）

気道周囲　（ なし ・ あり ）
後頭部　（ なし ・ あり ）
上縦隔　（ なし ・ あり ）
肺　（ なし ・ あり → 左 ・ 右 ）

現在の身長・体重の測定日　（　　年　　月　　日）
現在の身長　（　　）SD　　現在の体重　（　　）SD

気道狭窄症状　（ なし ・ あり ）
胸水・腹水・リンパ液等の体液の喪失　（ なし ・ あり ）
骨病変　（ なし ・ あり → 骨病変部位：　　）

経口摂取困難　（ なし ・ あり ）
運動障害　（ なし ・ あり ）

その他の特記すべき症状　（ なし ・ あり → 詳細：　　）

2.検査所見

診断の根拠となった主な検査等の結果

該当するものに○をつけ、必要な場合には（ ）内に記載（数値を用いて具体的に）　継続は現在の状況を記載

画像検査（単純レントゲン写真、CT・MRI、超音波検査・胎児超音波検査、その他）

単純X線写真　（ 未実施 ・ 実施 → 所見：　　）
CT・MRI検査　（ 未実施 ・ 実施 → 所見：　　）
超音波検査　（ 未実施 ・ 実施 → 所見：　　）
その他の画像検査　（ 未実施 ・ 実施 → 所見：　　）

生化学的検査（嚢胞内液の所見など）

（ 未実施 ・ 実施 → 所見：　　）

病理診断（切除標本の所見）

（ 未実施 ・ 実施 → 所見：　　）

3.その他の所見

その他の現在の所見など

合併症　（ なし ・ あり → 詳細：　　）

4.経過

現在の治療

薬物療法　（ なし ・ あり → 詳細：　　）
現在の治療　（ なし ・ あり → 持続陽圧呼吸療法 ・ 人工呼吸管理 ・ 酸素療法 ・ 気管切開管理 ・ 気管挿管 ・ 中心静脈カテーテル留置 ・ 中心静脈栄養 ・ 経管栄養（腸瘻/胃瘻含む） ・ 外科的切除 ・ 硬化療法 ・ 蛋白補充療法 ・ 成分輸血療法 ・ その他（　　））

過去の主な治療・検査など

5.今後の療法方針

就学・就労	1. 就学前　2. 小中学校（通常学級・通級・特別支援学級）　3. 特別支援学校（小中学部・専攻科を含む高等部） 4. 高等学校（専攻科を含む）・高等専門学校・専門学校/専修学校など　5. 大学（短期大学を含む）　6. 就労（就学中の就労も含む） 7. 未就学かつ未就労　8. その他（　　）
現状評価	一つに○印 ： 治癒 ・ 寛解 ・ 改善 ・ 不変 ・ 再発 ・ 悪化 ・ 死亡 ・ 判定不能 小児慢性特定疾病 重症患者認定基準に該当： しない ・ する ・ 不明　　人工呼吸器等装着者認定基準に該当： しない ・ する ・ 不明
治療見込期間	入院　年　月　日 から　年　月　日 まで 通院　年　月　日 から　年　月　日 まで（ 月　回 ）

上記の通り診断します。

医療機関名
および
所在地

科

平成　年　月　日　　医師名

印

小児慢性特定疾病指定医番号

1212-1.0.1

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, Okuyama H, Kanamori Y, Nagata K, Hayakawa M, Inamura N, Takahashi S, Taguchi T.	The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias.	J Pediatr Surg	49(8)	1191-1196	2014
Usui N, Nagata K, Hayakawa M, Okuyama H, Kanamori Y, Takahashi S, Inamura N, Taguchi T.	Pneumothoraces as a fatal complication of congenital diaphragmatic hernia in the era of gentle ventilation.	Eur J Pediatr Surg	24(1)	31-38	2014
Nagata K, Usui N, Terui K, Takayasu H, Goishi K, Hayakawa M, Tazuke Y, Yokoi A, Okuyama H, Taguchi T.	Risk Factors for the Recurrence of the Congenital Diaphragmatic Hernia-Report from the Long-Term Follow-Up Study of Japanese CDH Study Group.	Eur J Pediatr Surg	E-pub	DOI: 10.1055/s-0034-1395486	2014
Terui K, Taguchi T, Goishi K, Hayakawa M, Tazuke Y, Yokoi A, Takayasu H, Okuyama H, Yoshida H, Usui N. The Japanese Congenital Diaphragmatic Hernia Study Group.	Prognostic factors of gastroesophageal reflux disease in congenital diaphragmatic hernia: a multicenter study.	Pediatr Surg Int	30(11)	1129-1134	2014
Shiono N, Inamura N, Takahashi S, Nagata K, Fujino Y, Hayakawa M, Usui N, Okuyama H, Kanamori Y, Taguchi T, Minakami H.	Outcomes of congenital diaphragmatic hernia with indication for Fontan procedure.	Pediatr Int	56(4)	553-558	2014
Inamura N, Kubota A, Ishii R, Ishii Y, Kawazu Y, Hamamichi Y, Yoneda A, Kawahara H, Okuyama H, Kayatani F.	Efficacy of Circulatory Management of Antenatally Diagnosed Congenital Diaphragmatic Hernia: Outcome of Proposed Strategy.	Pediatr Surg Int	30(9)	889-894	2014
Shibuya S, Ogasawara Y, Izumi H, Kantake M, Obinata K, Yoshida K, Lane GJ, Yamataka A, Okazaki T.	A case of congenital diaphragmatic hernia with intradiaphragmatic pulmonary sequestration: case report and literature review.	Pediatr Surg Int	30(9)	961-963	2014
Sakai K, Kimura O, Furukawa T, Fumino S, Higuchi K, Wakao J, Kimura K, Aoi S, Masumoto K, Tajiri T.	Prenatal administration of neuropeptide bombesin promotes lung development in a rat model of nitrofen-induced congenital diaphragmatic hernia.	J Pediatr Surg	49	1749-1752	2014
Yokota K, Uchida H, Kaneko K, Ono Y, Murase N, Makita S, Hayakawa M.	Surgical complications, especially gastroesophageal reflux disease, intestinal adhesion obstruction, and diaphragmatic hernia recurrence, are major sequelae in survivors of congenital diaphragmatic hernia.	Pediatr Surg Int	30(9)	895-899	2014

Ono S, Maeda K, Baba K, Usui Y, Tsuji Y, Kawahara I, Fukuta A, Sekine S.	Balloon tracheoplasty as initial treatment for neonates with symptomatic congenital tracheal stenosis	Pediatr Surg Int	30(9)	957-960	2014
藤野明浩、高橋信博、石濱秀雄、藤村　匠、加藤源俊、富田紘史、渕本康史、星野　健、黒田達夫	気管周囲を取り巻く頸部・縦隔リンパ管腫切除	小児外科	46(2)	105-110	2014
藤野明浩、森定　徹、梅澤昭弘、黒田達夫	ヒトリンパ管腫モデル動物の作成	小児外科	46(6)	635-638	2014
藤野明浩、上野　滋、岩中　督、木下義晶、小関道夫、森川康英、黒田達夫	リンパ管腫	小児外科	46(11)	1181-1186	2014
小関道夫	複数の診療科で遭遇しうる「リンパ管腫症」の実態	日経メディカル		7月25日号	2014

IV. 研究成果の刊行物・別刷

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Original Articles

The lung to thorax transverse area ratio has a linear correlation with the observed to expected lung area to head circumference ratio in fetuses with congenital diaphragmatic hernias

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ABSTRACT

Background/Purpose: The purpose of this study was to clarify the relationship between the lung to thorax transverse area ratio (L/T ratio) and the observed to expected lung area to head circumference ratio (O/E LHR), based on the results of a nationwide Japanese survey conducted in 2011, and to evaluate the compatibility of these prognostic predictors of fetal CDH.

Methods: Two hundred and forty-two prenatally diagnosed isolated CDH patients born between 2006 and 2010 were included in the present analysis. A regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on 191 simultaneous measurements of these parameters in 120 patients.

Results: The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233 + (0.00222 × O/E LHR), ($R = 0.847$, $p < 0.0001$). According to this equation, 25% of the O/E LHR, the cut-off value used in the fetal intervention for CDH, was equivalent to an L/T ratio of 0.08, a commonly accepted cut-off value for identifying the most severe cases of fetal CDH.

Conclusions: As there is a positive correlation between the L/T ratio and the O/E LHR, these two parameters proved to be used interchangeably according to the linear regression equation.

The mortality and morbidity of infants with congenital diaphragmatic hernia (CDH) mainly depend on the severity of pulmonary hypoplasia. Therefore, an accurate prenatal assessment of pulmonary hypoplasia is necessary to establish an optimal treatment strategy for individuals before birth. Although many prenatal prognostic parameters have previously been proposed by various investigators [1–4], measurement of the residual lung size seems to be one of the most reasonable and realistic methods [5–8].

The lung area to head circumference ratio (LHR) was the most commonly used predictor for CDH in the past [5,9,10]. The observed to expected (O/E) LHR has become a standard parameter used for determining the indications for fetal intervention to treat severe cases of CDH [11]. Of note, the O/E LHR was used in the Tracheal Occlusion To Accelerate Lung growth (TOTAL) trial of left CDH patients with severe pulmonary hypoplasia [12,13]. On the other hand, the lung to thorax transverse area ratio (L/T ratio), which was proposed before the publication of the LHR [5,6,9], has been widely used in Japan for the assessment of pulmonary hypoplasia in fetal CDH patients [6,14–16]. The LHR is no longer considered to be independently predictive of survival [17,18], as it was shown to increase according to the gestational age [11,19–21]. In contrast, the O/E LHR is not influenced by gestational age [22] as is the case with the L/T ratio [6,14,19], because it is standardized by the normal mean value of the LHR corresponding to the specific gestational age [11]. Both of the indicators are similarly based on the measurement of the contralateral lung area by using tracing methods [6,21,23] at the transverse section containing the four-chamber view of the heart.

The relationship between the L/T ratio and the O/E LHR has not been studied, despite their similarities. The purpose of this study was to clarify the relationship between the L/T ratio and the O/E LHR and to evaluate the compatibility of these parameters as prognostic predictors of fetal CDH based on the results of a nationwide Japanese survey.

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1. Materials and methods

1.1. Study population

This retrospective cohort study was performed as part of a nationwide Japanese survey of neonatal CDH conducted in 2011. This study was conducted after being approved by the ethics committee of Osaka University Hospital (approval number 11017) and the independent ethics committees of five other participating institutions: Hyogo College of Medicine, National Center for Child Health and Development, Kyushu University, Nagoya University Hospital and Osaka Medical Center and Research Institute for Maternal and Child Health. The data obtained from 72 institutions that consented to participate in a questionnaire survey targeted to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals were retrospectively evaluated. Data were collected as case report forms requesting further details about the patients by the data center located in Osaka University Graduate School of Medicine. The entered data were crosschecked twice by the data center and then were fixed after data cleansing. A total of 614 neonates with CDH were born between 2006 and 2010; the overall profiles of the patients are described elsewhere [24]. Among those subjects, the present study was conducted using the data of the 364 isolated CDH cases that were prenatally diagnosed.

Isolated CDH was defined as being present in CDH infants who did not have other serious congenital anomalies, such as major cardiac anomalies or unfavorable chromosomal abnormalities. Three cases of bilateral diaphragmatic hernia were excluded from the study. The contralateral lung area accompanied by the thorax area and/or the head circumference was measured at least one time in 242 out of the 364 cases. The initial and final measurements were reported in the case report form if those parameters were measured more than two times. A total of 242 study subjects (400 measurements), which accounted for 39.4% of all 614 CDH patients treated at 45 institutes, were ultimately included in the present analysis. Among those subjects, the thorax area measurement was reported 339 times for 210 patients and the head circumference measurement was reported 251 times for 154 patients. The contralateral lung area, the thorax area and the head circumference were simultaneously measured 191 times in 120 patients.

1.2. Collected data

The primary outcome measure was the survival to discharge, which was defined as surviving at the time of discharge from the hospital. The secondary outcome measure was the "intact discharge", which is a new concept for prognostic evaluation, defined as being discharged from the hospital without any major morbidity that requires home treatment, including ventilatory support, oxygen administration, tracheostomy, tube feeding, parenteral nutrition or vasodilator administration [4]. The patient demographics, including the gestational age, birth weight, Apgar score at 1 minute, presence of liver and stomach herniation, mode of delivery, gender and side of hernia, were reviewed. Whether a surgery could be performed, the size of the diaphragmatic defect, the surgical procedure performed, the use of high-frequency oscillatory ventilation (HFOV), nitric oxide inhalation (iNO), prostaglandin E_1 or extracorporeal membrane oxygenation (ECMO) were also reviewed. As the indication criteria for surgery were not defined prospectively, the operability of each case was determined according to the clinical decisions of each institution. The highest preductal PaO_2, best oxygenation index and the right to left shunting at the ductus which were determined within 24 h after birth, were reviewed. The contralateral lung area (in square millimeters) and the thorax area (in square millimeters) were measured by manual tracing of the limit of the lung and thorax at the transverse section containing the four-chamber view of the heart in ultrasonography. The head circumference (in millimeters) was measured in the standard biparietal view of ultrasonography. The L/T ratio was defined as the area of the contralateral lung divided by the area of the thorax [19]. The observed LHR, which was the ratio of the contralateral lung to the head circumference, was divided by the appropriate normal mean for gestational age and multiplied by 100 to derive the O/E LHR and expressed as a percentage [21]. The expected LHRs were determined by the published formulas, which are freely available to all by the official calculator in the Tracheal Occlusion To Accelerate Lung Growth (TOTAL) trial website (access http://www.totaltrial.eu/) [12].

1.3. Analysis of the relationship between the L/T ratio and the O/E LHR

A simple regression analysis was conducted to investigate the relationship between the L/T ratio and the O/E LHR based on the simultaneous measurements in 120 cases. Although the initial and final simultaneous measurements were available in 71 cases, only a single simultaneous measurement was available in 49 cases. We decided to use all simultaneous measurements in order to obtain more accurate relationships between the two parameters. The linear regression equation between the L/T ratio and the O/E LHR was derived from the regression analysis. The L/T ratio values which corresponded to the cut-off values of the O/E LHR used in the TOTAL trial entry criteria were calculated according to the linear regression equation.

1.4. Patient outcome according to the prenatal prediction of the disease severity

In the 226 cases of left isolated CDH whose liver herniation was evaluated, the survival to discharge rate was reviewed according to the classification of the disease severity used in the TOTAL trial, which was defined by the combination of the O/E LHR and the presence of liver herniation, as proposed by Deprest et al. [25]. In the cases whose O/E LHR was not measured, the O/E LHR was estimated from the L/T ratio using the linear regression equation. The patient demographics, prenatal and postnatal profiles, including parameters indicating the respiratory status, circulatory status, surgical findings and outcome, were compared among the prenatal risk-stratified classifications defined by the combination of the L/T ratio and the presence of liver herniation, as proposed by Usui et al. [16]. In the cases whose L/T ratio was not measured, the L/T ratio was estimated from the O/E LHR using the linear regression equation. The values of the O/E LHR and L/T ratio were represented by the initial values of two measurements in principle, and the final values were substituted for the patients whose initial value was not available in the case report form.

1.5. Statistical analysis

The statistical analyses were performed using the JMP software program (version 9.02; SAS Institute, Inc, Cary, NC, USA). The frequencies and percentages were used to describe categorical data. The means and standard deviation were used to describe continuous variables. The median and interquartile ranges were used to describe Apgar scores. The chi-square test and Fisher's exact test were used to analyze categorical data. The one-way analysis of variance with Tukey's post-hoc honestly significant difference test was used to compare continuous variables. The Kruskal–Wallis test was used for the comparison of the Apgar scores. The log-rank test and Kaplan–Meier method were used to compare the survival times. Values of $P < 0.05$ were considered to indicate statistical significance.

2. Results

An outline of the patient demographics is shown in Table 1. Of the 242 neonates with prenatally diagnosed isolated CDH, 177 (73.1%)

Table 1
The patient demographics.

Number of patients	242
Gestational age (days)[a]	264.3 ± 8.6
Birth weight (g)[a]	2746 ± 386
Apgar score at 1 min[b]	4 (2–6)
Liver-up[c]	68/239 (28.5%)
Contralateral stomach herniation[d]	35/236 (14.8%)
Caesarean section delivery	177 (73.1%)
Gender (male)	138 (57.0%)
Side of hernia (left)	229 (94.6%)
Surgery performed for diaphragmatic hernia	224 (92.6%)
Time of surgery after birth (h)[b]	56, (30–95)
Patch closure	81/224 (36.2%)
Use of HFOV	212/233 (91.0%)
Use of iNO	166/241 (68.9%)
Use of ECMO	19 (7.9%)
Survival to discharge	200 (82.6%)
Intact discharge	177 (73.1%)

HFOV: high-frequency oscillatory ventilation, iNO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation.
[a] Mean ± standard deviation.
[b] Median (interquartile range).
[c] Liver-up, liver occupying more than one-third of the thoracic space.
[d] Contralateral stomach herniation, more than half of the stomach was herniating into the contralateral thoracic cavity.

were delivered by Caesarean section and 224 (92.6%) underwent surgical repair for diaphragmatic hernia at a median age of 56 h after birth. Surgery could not be performed in 18 cases (7.4%) based on the clinical decisions of each institution. It was therefore assumed that these cases were extremely unstable and were considered to be in too serious of a condition to undergo a surgical repair. Two hundred patients (82.6%) survived until discharge, 177 (73.1%) of whom were discharged from the hospital without any major morbidity that required home treatment (Table 1).

2.1. Relationship between the L/T ratio and the O/E LHR

Eighteen of the 120 infants whose L/T ratio and O/E LHR were simultaneously determined died, resulting in an 85.0% survival rate. We found a strong positive correlation between the L/T ratio and the O/E LHR. The linear regression equation between the L/T ratio and the O/E LHR was: L/T ratio = 0.0233 + (0.00222 × O/E LHR), where the regression coefficient was 0.00222, correlation coefficient was 0.847 and coefficient of determination was 0.717 ($p < 0.0001$) (Fig. 1). According to this equation, 15%, 25%, 35% and 45% of the O/E LHRs, the cut-off values used in the TOTAL trial of left CDH patients, were found to be equivalent to 0.06, 0.08, 0.10 and 0.12 L/T ratios, respectively.

2.2. Patient outcome according to the prenatal prediction of the disease severity

In the 226 cases of left isolated CDH, the survival to discharge rate was reviewed according to the four-step stratification proposed by Deprest et al. [25]. The survival rate exhibited a trend toward a decrease as the severity of the disease increased. However, the effect of the liver herniation seemed to be stronger in our series compared to those in the series described by Deprest et al. (Fig. 2). In the prenatal risk-stratified classification [16], there were no significant differences in the patient demographics except for the side of hernia. There were unsurprisingly significant differences in the rate of liver-up and the L/T ratio based on how the each group was defined (Table 2). The highest preductal PaO_2 decreased, and the best oxygenation index increased, as the severity of the disease increased. The right to left shunting at ductus evaluated within 24 h after birth, which suggests the severity of pulmonary hypertension, differed significantly among the three groups, which resulted in the differences in the numbers of patients who used iNO, prostaglandin E_1 and ECMO. Although surgical repair

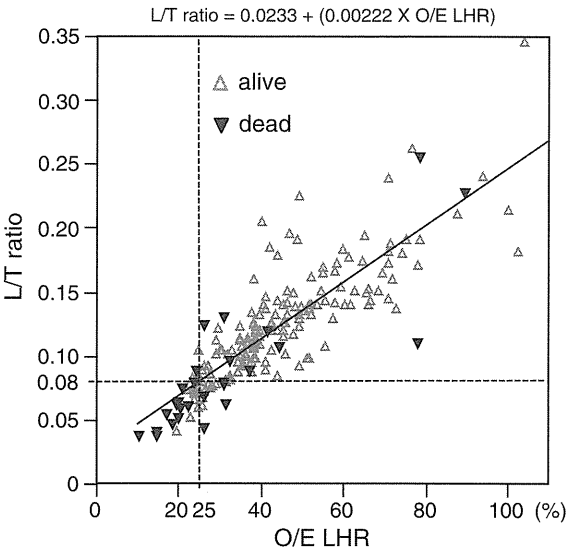

Fig. 1. The relationship between the O/E LHR and the L/T ratio. There was a linear positive correlation between the L/T ratio and the O/E LHR. The linear regression line was: L/T ratio = 0.0223 + (0.00222 × O/E LHR), where the regression coefficient was 0.00222, the correlation coefficient was 0.847 and the coefficient of determination was 0.717 ($p < 0.0001$). The open triangles represent the survivors and the closed triangles represent the non-survivors. The 25% O/E LHR was equivalent to an L/T ratio of 0.08 according to this equation, as indicated by broken lines.

could not be performed in only two (1.3%) cases in group A, surgery was not possible in six out of 16 (35.3%) cases in group C due to their unstable conditions. There were also significant differences in the proportions of patients with diaphragmatic defects exceeding 75%, as rated by the surgical record, as well as the need for patch repair. There were significant differences in the morbidity and mortality among the three groups. The rate of survival to discharge was 93% and the intact discharge rate was 87% in group A, whereas the corresponding rates were 72% and 58% in group B and 35% and 18% in group C, respectively (Table 3). There were also statistically significant differences in the survival curves among the three groups (Fig. 3).

3. Discussion

Since the mortality and morbidity of neonates with CDH primarily depend on the severity of pulmonary hypoplasia, an accurate prenatal assessment of pulmonary hypoplasia is necessary for making a decision about the optimal treatment. Although many prenatal prognostic parameters have been reported previously [1–4], the assessment of the residual lung size seems to be one of the most reasonable and

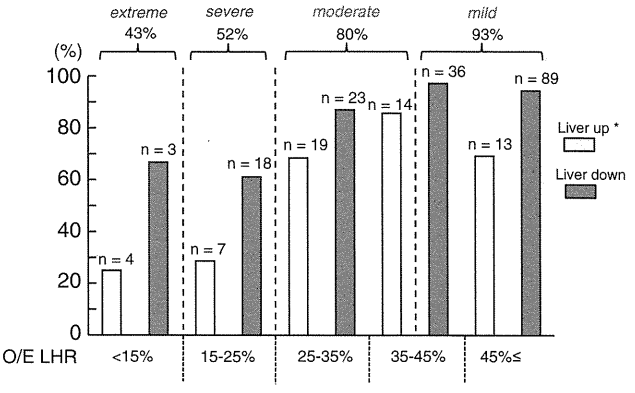

Fig. 2. The survival rates depending on the O/E LHR measurements and presence of liver herniation. *Liver-up, liver occupying more than one-third of the thoracic space.

Table 2
The patient demographics and prenatal findings according to the prenatal risk-stratified classification [16].

Definition of the group [16]	Group A	Group B	Group C	P
	L/T ratio ≥ 0.08 with liver-down	L/T ratio ≥ 0.08 with liver-up[a] or L/T ratio < 0.08 with liver-down	L/T ratio < 0.08 with liver-up[a]	
Number of patients	151	71	17	
Gender (male)	89 (58.9%)	36 (50.7%)	12 (70.6%)	0.265
Side of hernia (left)	149 (98.7%)	64 (90.1%)	13 (76.5%)	< 0.001
Gestational age at birth (days)	265 ± 7.7	263 ± 10.6	264 ± 6.9	0.313
Birth weight (kg)	2.76 ± 0.37	2.68 ± 0.45	2.87 ± 0.26	0.141
Caesarian section delivery	109 (72.2%)	53 (74.7%)	12 (70.6%)	0.908
Liver-up[a]	0 (0.0%)	51 (71.8%)	17 (100%)	< 0.001
Contralateral stomach herniation	5/148 (3.4%)	20/71 (28.2%)	10/17 (58.8%)	< 0.001
L/T ratio	0.148 ± 0.053*	0.106 ± 0.039**	0. 059 ± 0.020***	< 0.001

[a] Liver-up, liver occupying more than one-third of the thoracic space; Contralateral stomach herniation, more than half of the stomach was herniating into the contralateral thoracic cavity; L/T ratio, contralateral lung to thorax transverse area ratio.
* $P < .05$ A vs B.
** $P < .05$ B vs C.
*** $P < .05$ C vs A.

realistic methods. It has previously been reported that the LHR, which was first described in 1996 [5], was increased according to the gestational age in normal fetuses [21] and also in the fetuses with CDH [11,19]. The reason for this increase in the LHR with the gestational age is due to the difference in the rate of the increase of the lung area and head circumference. Peralta et al. reported that there was a four-fold increase in the LHR between 12 and 32 weeks of gestation in normal fetuses because of these differences [21]. Approaches to standardize the LHR by using the normal mean value of the LHR have been proposed to provide a constant value throughout the gestational period [11]. The LHR was originally defined as the contralateral lung area determined using a two-dimensional perpendicular linear measurement, divided by the head circumference [5]. However, two other methods to determine the lung area were subsequently proposed [9,21], and the tracing method was finally found to be the most reproducible method to measure the lung area [21,23].

The L/T ratio has been widely used in Japan, because it was first described in 1990 for the assessment of pulmonary hypoplasia in CDH [6], and has been applied for the assessment of pulmonary hypoplasia in CDH neonates since then [15,16,26]. The L/T ratio was originally reported to be constant throughout the gestational period in normal fetuses [6]. This parameter was redefined as the contralateral lung area, to make it more consistent with the LHR, divided by the area of the thorax as measured by the tracing method [19], although the original definition was determined by using the area of both lungs. Thus, there are several similarities between these two parameters. First, both parameters exhibit constant values throughout the gestational period, and the other is that only the contralateral lung area is measured by using the tracing method. However, the relationship between these two parameters has not been studied, despite their similarities.

A strong positive correlation between the L/T ratio and the O/E LHR was found, and a linear regression equation between the L/T ratio and the O/E LHR was obtained. According to this linear regression equation, several important cut-off values of both parameters can be interchanged. Interestingly, a 25% O/E LHR, the cut-off value for the most severe cases as used in the TOAL trial for fetal CDH, was found to be equivalent to an L/T ratio of 0.08, a commonly accepted cut-off

Table 3
The respiratory status, circulatory status, intraoperative findings and outcomes according to the prenatal risk-stratified classification [16].

Definition of the group [16]	Group A	Group B	Group C	P
	L/T ratio ≥ 0.08 with liver-down	L/T ratio ≥ 0.08 with liver-up[a] or L/T ratio < 0.08 with liver-down	L/T ratio < 0.08 with liver-up[a]	
Number of patients	151	71	17	
Apgar score at 1 min	5 (3–7) (n = 143)	4 (2–5) (n = 66)	2.5 (1.25–4) (n = 16)	<0.001
Highest preductal PaO_2 (Torr)[b]	257 ± 134* (n = 145)	199 ± 135** (n = 69)	75 ± 70*** (n = 17)	<0.001
Best oxygenation index[b]	5.7 ± 5.9* (n = 143)	14.3 ± 17.5** (n = 68)	32.0 ± 24.5*** (n = 17)	<0.001
Right to left shunting at ductus[b]	55/143 (38.5%)	40/68 (58.8%)	13/17 (76.5%)	0.001
Use of HFOV	130/145 (89.7%)	64/69 (92.8%)	16/17 (94.1%)	0.680
Use of iNO	85/151 (56.3%)	63/71 (88.7%)	15/16 (93.8%)	<0.001
Use of prostaglandin E_1	45/149 (30.2%)	35/71 (49.3%)	14/17 (82.4%)	<0.001
Use of ECMO	4 (2.7%)	9 (12.7)	5 (29.4%)	<0.001
Inoperable cases	2 (1.3%)	10 (14.1%)	6 (35.3%)	<0.001
Diaphragmatic defects ≥ 75%[c]	27/149 (18.1%)	38/61 (62.3%)	8/11(72.7%)	<0.001
Patch closure	31/149 (20.8%)	40/61 (65.6%)	8/11 (72.7%)	<0.001
Survival to discharge	141 (93.4%)	51 (71.8%)	6 (35.3%)	<0.001
Intact discharge	131 (86.8%)	41 (57.8%)	3 (17.7%)	<0.001

HFOV, high-frequency oscillatory ventilation, iNO, nitric oxide inhalation; ECMO, extracorporeal membrane oxygenation.
[a] Liver-up, liver occupying more than one-third of the thoracic space.
[b] The highest pre PaO_2, best oxygenation index and the right to left shunting at ductus were determined within 24 h after birth.
[c] The size of the diaphragmatic defect was rated by a surgeon according to the surgical record.
* $P < .05$ A vs B.
** $P < .05$ B vs C.
*** $P < .05$ C vs A.

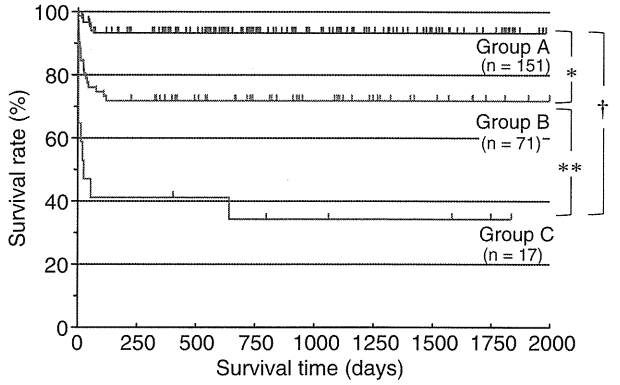

Fig. 3. The survival curves for patients with isolated CDH, compared using the prenatal risk-stratified classification [16]. *$P < .001$; **$P < .001$; †$P < .001$.

value for identifying the most severe cases of fetal CDH in Japan. These results suggested that the patients considered to be the most severe cases in Japan also met the criteria for fetal intervention for left CDH patients with severe pulmonary hypoplasia in the TOTAL trial protocol, which was the first international prospective randomized controlled trial for fetoscopic tracheal occlusion [12,13]. In the nationwide Japanese survey for fetal CDH, 57.7% of the patients were measured for the L/T ratio, and only 42.3% of the patients were measured for the O/E LHR. However, owing to this conversion equation, both of the parameters can be generated for the evaluation of the patient CDH severity if either of the parameters was measured.

To verify the accuracy and the universal applicability of the prenatal risk-stratified classification, which was proposed by Usui et al., and was defined as the combination of the L/T ratio and the presence of liver herniation [16], we applied the classification to this cohort as a different population from the original cohort using the conversion equation. Although the patient demographics except for the side of the hernia, were similar between the three groups classified using this system, the prenatal and postnatal profiles, including the stomach position, parameters indicating the respiratory status, circulatory status, surgical findings and outcome were significantly different between the three groups, suggesting that the prenatal risk-stratified classification is also valid in other cohorts, such as that in the nationwide Japanese questionnaire survey. The indication for a fetal intervention of the patients proposed by Deprest et al. [25] can be estimated by using the conversion eq. in the patients whom the L/T ratio was solely measured without measurement of LHR. The rate of survival to discharge was 93% in the mild group, 80% in the moderate group, 52% in the severe group and 43% in the extreme group (Fig. 2). Compared to this four-step stratification used in the TOTAL trial, our prenatal risk-stratified classification therefore seems to have better discrimination of disease severity. It is possible to describe the prenatal risk-stratified classification as shown in Table 4 using the O/E LHR instead of the L/T ratio according to the linear regression equation (Table 4).

When the characteristics of both parameters were compared, the gestational variation and the procedure of the lung area measurements were similar. However, there were concerns that the individual fetal growth variation is not considered when determining the O/E LHR. There may be a possibility for an overestimation in a small-for-date fetus, as the O/E LHR of these fetuses, which should have a lower LHR compared to an appropriate-for-date fetus, would be evaluated based on the normal mean value. The L/T ratio includes, by nature, individual fetal growth variation, and it can be determined with standard values for gestational age or with for a relevant population. More importantly, calculating the L/T ratio is a simple task to perform.

A major limitation of this study is that it was conducted in a retrospective manner using a questionnaire. Many of the institutions had a small number of cases, and the treatment strategies, including the indication criteria for surgery, were determined by each institution. There may have been inaccurate measurement of both parameters due to the limited experience of the physicians with such infants. More accurate prospective studies and an analysis of the correlation based on the timing of the measurement are therefore needed to confirm the present findings. Despite these limitations, an excellent positive correlation was observed between the L/T ratio and O/E LHR in the present study, and these two parameters proved to be compatible according to a linear regression equation. These results suggested that the linear regression equation may become a useful tool for all populations.

Table 4
The prenatal risk-stratified classification described using the O/E LHR instead of the L/T ratio.

Group A	O/E LHR ≥ 25% with liver-down
Group B	O/E LHR ≥ 25% with liver-up [a], or O/E LHR < 25% with liver-down
Group C	O/E LHR < 25% with liver-up [a]

[a] Liver-up, liver occupying more than one-third of the thoracic space.

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Pneumothoraces As a Fatal Complication of Congenital Diaphragmatic Hernia in the Era of Gentle Ventilation

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Abstract

Introduction Pneumothorax remains a life-threatening complication that occurs in congenital diaphragmatic hernia (CDH), even under respiratory management with gentle ventilation. The aim of this study was to evaluate the prevalence of pneumothoraces as a fatal complication during the management of CDH based on the results of a nationwide Japanese survey conducted in the era of gentle ventilation.

Materials and Methods A retrospective cohort study was performed as part of a nationwide Japanese survey of CDH. A total of 510 neonates with isolated CDH born between 2006 and 2010 were included in this study. The patients were divided into four groups according to operative findings related to the diaphragmatic defect size and operability, which represents the disease severity: defects less than 25%, defects more than 25% but less than 75%, defects more than 75%, and a patient group that was unable to undergo surgery. The prevalence of pneumothorax and the survival rate were compared with respect to each disease severity group. Each case was evaluated to determine whether the development of a pneumothorax was the primary cause of death.

Results Of the 510 neonates with isolated CDH, 69 patients developed a pneumothorax before and/or after surgical intervention. Of the 69 patients 38 patients died, and only 26 patients were discharged from the hospital without any major morbidity that requires home treatment ("intact discharge"). The prevalence of pneumothorax increased and the survival rate and intact discharge rate decreased as the severity of the disease worsened. The number of patients whose pneumothorax was presumed to

Keywords
- congenital diaphragmatic hernia
- pneumothorax
- gentle ventilation
- lung injury
- pulmonary hypoplasia

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be the primary cause of death also increased as the severity of the disease worsened. The survival rate of the patients with pneumothorax was significantly lower than that of the patients without pneumothorax among the groups with 25 to 75% defects and 75% or more defects.

Conclusions Pneumothoraces was found to more likely occur in neonates with CDH associated with a large defect of the diaphragm. The survival rate and intact discharge rate decreased as the severity of the disease worsened, especially among the patients who developed pneumothorax accompanied by large diaphragmatic defects. No other risk factors related to pneumothorax occurrence were found, except for the severity of the disease itself, thus suggesting that pneumothorax was associated with a lethal outcome in neonates with CDH associated with a large defect of the diaphragm.

Introduction

Congenital diaphragmatic hernia (CDH) remains one of the most challenging neonatal diseases facing neonatologists and pediatric surgeons, as it continues to be associated with a high mortality and morbidity due to pulmonary hypertension and pulmonary hypoplasia. Over the past several decades, there have been advances in treatment strategies including extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), and fetal interventions that have improved the outcomes of CDH patients. However, CDH patients exhibit a broad range of disease severity depending on the components of pulmonary hypertension and pulmonary hypoplasia, which directly affects mortality and morbidity.

Accumulating evidence has shown that ventilator-induced lung injury caused by hyperventilation can have a significant negative impact on short-term outcomes[1,2] and long-term pulmonary sequelae[3,4] in neonates with CDH. To prevent the negative effects of hyperventilation, "gentle ventilation" strategies based on the concept of permissive hypercapnia and permissive hypoxia have been adopted as standard protocol for the treatment of neonatal CDH in many institutions.[5–9] However, even under treatment with a gentle ventilation strategy, the incidence of pneumothorax occurrence, a life-threatening preoperative and/or postoperative complication, reportedly remains high, with rates ranging from 18 to 36%.[10–13] The aim of this study was to evaluate the prevalence of pneumothorax as a fatal complication during the management of CDH and to analyze factors contributing to the development of pneumothoraces based on the results of a nationwide Japanese survey conducted in the era of gentle ventilation strategies.

Materials and Methods

Patient Selection

This retrospective cohort study was performed as part of a nationwide survey of neonatal CDH conducted in 2011 with the support of the Ministry of Health, Labor and Welfare of Japan.[14] The study was performed after being approved by the ethics committee of Osaka University Hospital (approval number of 11017) and the independent ethics committees of five other participating institutions: Hyogo College of Medicine, National Center for Child Health and Development, Kyushu University, Nagoya University Hospital, and Osaka Medical Center and Research Institute for Maternal and Child Health. Data obtained from 72 institutions that consented to participate in a questionnaire survey targeted to the departments of pediatric surgery and/or tertiary perinatal care centers of 159 educational hospitals were retrospectively evaluated. Data were collected as case report forms requesting further details about the patients by the data center that was located in Osaka University Graduate School of Medicine. The entered data were cross-checked twice by the data center and then were fixed after data cleansing. A total of 614 neonates with CDH were born between 2006 and 2010; the overall profiles of the patients are described elsewhere.[14] This study was conducted using only the data of 520 isolated CDH cases defined as CDH infants who did not have serious congenital anomalies, such as major cardiac anomalies or unfavorable chromosomal abnormalities. Four patients with no description of the development of a pneumothorax and six patients whose diaphragmatic defect size was not rated by a surgeon were excluded from this study. Therefore, 510 patients with isolated neonatal CDH were ultimately included in the following analysis.

Data Collection

The primary outcome measure was the occurrence of pneumothorax independent of surgical repair of the diaphragm. We defined pneumothorax as an air leakage from the lungs which was diagnosed by chest X-rays. The cases of preoperative and/or postoperative pneumothorax and of ipsilateral, contralateral, and bilateral pneumothoraces were all included in the primary outcome measures. The secondary outcome measures were survival to discharge, defined as surviving until the time of discharge from the hospital, and "intact discharge," which is a new concept for prognostic evaluation, defined as being discharged from the hospital without any major morbidity that requires home treatment including ventilatory support, oxygen administration, tracheotomy, tube feeding, parenteral nutrition, or vasodilator administration.[15] The patient demographics, including gestational age,

birth weight, Apgar score at 1 minute, prenatal diagnosis with findings of liver herniation, and lung-to-thorax transverse area ratio,[16] mode of delivery, gender, and side of hernia, were reviewed. Whether a surgery could be performed, the incidence of right-to-left shunting at the ductus within 24 hours after birth and the use of HFOV, iNO, or ECMO were also reviewed. As arterial blood gas data, the highest Pao_2 within 24 hours after birth, including the ventilator settings and the lowest $Paco_2$ within 24 hours after birth were analyzed. Although the blood gas data were in principle obtained from the preductal artery, data for the postductal artery were substituted in patients whose preductal arterial data were not available.

Stratification According to Disease Severity

Among the patients who underwent surgical intervention for a diaphragmatic hernia, the time of surgery after birth, diaphragmatic defect size, and operative method were reviewed. The diaphragmatic defect size was rated by a surgeon to evaluate and classify the severity of disease based on the three levels. The patients were divided into four groups according to operative findings related to the diaphragmatic defect size and operability: defects less than 25%, defects more than 25% but less than 75%, defects more than 75%, and a patient group that was unable to undergo surgery. The prevalence of pneumothorax was compared between the disease severity groups. Each case was evaluated to determine whether the development of pneumothorax was the primary cause of death using a questionnaire. In each subgroup having the same severity of disease, several parameters related to pneumothorax occurrence were compared between the patients who developed pneumothorax and those who did not.

Statistical Analysis

The statistical analyses were performed using the JMP software program (version 9.02; SAS Institute, Inc, Cary, North Carolina, United States). The mean and standard deviation or median and interquartile range were used to describe continuous variables. The frequency and percentages were used to describe categorical data. Student *t*-test and an analysis of variance were used to compare continuous variables. The χ^2 test and Fisher exact test were used to analyze categorical data. *p* values of less than 0.05 were considered to indicate statistical significance.

Results

Prevalence of Pneumothorax and the Survival Rate

An outline of the patient demographics is shown in ►Table 1. Of the 510 neonates with isolated CDH, 361 (70.8%) neonates were diagnosed prenatally and 471 (92.4%) neonates underwent surgical repair for diaphragmatic hernia at a median age of 56 hours after birth. A total of 429 patients (84.1%) survived until discharge, 380 (74.5%) patients of whom were discharged from the hospital without any major morbidity that requires home treatment. (►Table 1).

Table 1 Patient demographics

Patient number	510
Gestational age (d), mean ± SD	265.4 ± 13.8
Birth weight (g), mean ± SD	2,645 ± 452
Apgar score at 1 min, median (interquartile range)	5 (3–7.3)
Prenatal diagnosis, (%)	361 (70.8)
Liver-up, (%)	86/339 (25.4)
L/T ratio < 0.08 (equivalent of o/e LHR < 25%), (%)	57/200 (28.5)
Caesarean section at delivery, (%)	309 (60.6)
Gender (male), (%)	287 (56.3%)
Side of hernia (left/right/both)	463/44/3
Surgery performed for diaphragmatic hernia, (%)	471 (92.4)
Time at surgery after birth (h), median (interquartile range)	56 (28–96)
Patch closure, (%)	118/471 (25.1)
Use of HFOV, (%)	367 (78.9)
Use of iNO, (%)	282 (55.4)
Use of ECMO, (%)	37 (7.3)
Survival to discharge, (%)	429 (84.1)
Intact discharge, (%)	380 (74.5)

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; o/e LHR, observed-to-expected lung area-to-head circumference ratio; SD, standard deviation.

Of the 510 neonates with isolated CDH, 69 (13.5%) neonates developed a pneumothorax before and/or after surgical intervention. Of the 69 patients, 38 (55.1%) patients died and only 26 (37.7%) patients were discharged from the hospital without any major morbidity that requires home treatment. The prevalence of pneumothorax increased as the severity of disease, represented by the operative findings, worsened. Indeed, the prevalence of pneumothorax in the inoperable group was 46%, whereas that observed in the less than 25% defects group was only 2%. The number of patients whose pneumothorax was presumed to be the primary cause of death increased as the severity of the disease increased. Approximately 40% of the patients died of pneumothorax in both the 75% or more defects group and the inoperable group (►Table 2). The survival to discharge rate and intact discharge rate decreased in association with the size of the diaphragmatic defects, and all patients in the inoperable group died. The survival rate was significantly lower in the patients who developed pneumothorax compared with that observed in the patients who did not develop a pneumothorax among the patients with 25 to 75% defects. In the 75% or more defects group, the survival-to-discharge rate as well as the intact discharge rate was significantly decreased among the patients who developed pneumothorax (►Table 2).

Table 2 Incidence and outcomes of pneumothorax occurrence according to the disease severity evaluated based on the operative findings

	< 25% defects	25–75% defects	≥ 75% defects	Inoperable cases	*p*
Patient number, *n*	87	259	125	39	
Pneumothorax, *n* (%)	2 (2)	23 (9)	26 (21)	18 (46)	< 0.001
Pneumothorax as primary cause of death, *n* (%)	0 (0)	2 (9)	10 (38)	8 (44)	0.035
Survival to discharge, *n* (%)	87 (100)	251 (97)	91 (73)	0 (0)	< 0.001
Survival without pneumothorax, *n* (%)	85 (100)	232 (98)[a]	81 (82)[a]	0 (0)	< 0.001
Survival with pneumothorax, *n* (%)	2 (100)	19 (83)[a]	10 (38)[a]	0 (0)	< 0.001
Intact discharge, *n* (%)	87 (100)	228 (88)	67 (54)	0 (0)	< 0.001
Intact discharge without pneumothorax, *n* (%)	85 (100)	210 (89)	61 (62)[a]	0 (0)	< 0.001
Intact discharge with pneumothorax, *n* (%)	2 (100)	18 (78)	6 (23)[a]	0 (0)	< 0.001

[a] $p < 0.01$, with pneumothorax versus without pneumothorax.

Analysis of Risk Factors for the Development of Pneumothorax

In the 25 to 75% defects group, the best oxygenation index within 24 hours after birth was higher and a higher mean airway pressure was required in the patients who developed a pneumothorax compared with that observed in the patients who did not. This may be related to the higher incidence of persistent pulmonary hypertension of the neonate (PPHN), determined based on the incidence of right-to-left shunting at the ductus, in the patients with pneumothorax compared with that observed in patients without pneumothorax. The higher incidence of PPHN resulted in higher rates of iNO and ECMO use in the patients with a pneumothorax compared with those observed in the patients without a pneumothorax (►Table 3).

Patients in the 75% or more defect group showed a higher best oxygenation index and a higher rate of patch closure compared with the patients in the 25 to 75% defects group regardless of pneumothorax occurrence (►Table 3 and ►Table 4). In the 75% or more defects group, there were no significant differences in the parameters, except for a slight difference in the rate of iNO use between the patients who developed pneumothorax and the patients who did not (►Table 4). Inoperable patients clearly showed a lower highest Pao_2, a higher lowest $Paco_2$, and a higher best oxygenation index, thus suggesting a more severe condition of the disease, compared with the patients in the 75% or more defect group without reference to pneumothorax occurrence (►Table 4 and ►Table 5). No significant differences were observed in any parameter between the patients with a pneumothorax and the patients without pneumothorax among the inoperable patients. These patients died at a median age of 2 days after birth regardless of pneumothorax occurrence (►Table 5).

Discussion

Before the mid-1990s, the use of hyperventilation to induce alkalosis was the mainstay of respiratory management for the treatment of PPHN in neonates with CDH, as it was believed that alkalosis could reverse or eliminate ductal shunting by decreasing pulmonary vascular resistance and pulmonary artery pressure.[17] However, subsequent evidence demonstrated that ventilator-induced lung injury caused by hyperventilation could have a significant impact on the survival statistics,[1,2] as well as the long-term pulmonary function, in infants with CDH.[3,4] A large single-center retrospective series of nonsurvivors with CDH treated with a hyperventilation strategy showed that 62 of 68 cases (91%) exhibited evidence of diffuse alveolar damage with hyaline membrane formation, 44 of 62 cases (65%) exhibited evidence of pneumothorax, and 35 of 68 (51%) cases exhibited evidence of parenchymal hemorrhage. Sakurai et al suggested that a significant degree of lung injury was related to a high peak inspiratory pressure and that ventilator-induced lung injury plays an important role in the mortality of patients with CDH.[2]

A permissive hypercapnia strategy was advocated for ventilation in infants with PPHN more than 25 years ago.[18] To prevent the negative effect of hyperventilation in the respiratory management of CDH, a permissive hypercapnia strategy was adopted for neonates with CDH at several institutions in the late 1990s. Case series of CDH have shown that airway pressure limitation and tolerance of hypercapnia, with a focus on preductal oxygen saturation, are the most important factors favorably influencing outcomes.[5–9] The widespread use of iNO therapy from the mid-1990s, which had a selective effect on decreasing pulmonary vascular resistance and pulmonary artery pressure, may have contributed to the switch from hyperventilation strategies to gentle ventilation strategies. Therefore, gentle ventilation strategies based on the concept of permissive hypercapnia and permissive hypoxia have become the mainstay of respiratory management for neonates with CDH. Although the survival rate has improved under the use of gentle ventilation strategies, the incidence of pneumothorax occurrence, a life-threatening preoperative and/or postoperative complication, reportedly

Table 3 Comparison of the parameters in the patients with 25–75% defects in the diaphragm

Development of pneumothorax	No (n = 236)	Yes (n = 23)	p
Gestational age (d), mean ± SD	267 ± 11	265 ± 9	0.521
Birth weight (g) , mean ± SD	2,804 ± 404	2,757 ± 399	0.589
Apgar score at 1 min, median (interquartile range)	6 (3–8)	4 (3–6)	0.054
Caesarean section at delivery, n (%)	141 (60)	16 (70)	0.503
Prenatal diagnosis, n (%)	162 (69)	20 (87)	0.093
Liver-up, n/N (%)	15/149 (10)	2/20 (10)	1.000
L/T ratio < 0.08, n/N (%)	15/85 (18)	3/11 (27)	0.427
Use of HFOV, n/N (%)	156/215 (73)	22/23 (96)	0.053
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	235 ± 142	194 ± 122	0.183
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	35 ± 23	38 ± 16	0.548
Best oxygenation index within 24 h after birth, mean ± SD	5.5 ± 5.4	8.4 ± 7.6	0.022[a]
Mean airway pressure (cmH_2O), mean ± SD	12.6 ± 2.9	14.2 ± 2.6	0.015[a]
Right-to-left shunting at ductus within 24 h after birth, n/N (%)	62/216 (29)	15/23 (65)	0.001[b]
Use of iNO, n/N (%)	107/235 (46)	18/23 (78)	0.004[b]
Use of ECMO, n/N (%)	5/236 (2)	3/23 (13)	0.026[a]
Time of surgery after birth (h), median (interquartile range)	52 (28–85)	76 (39–141)	0.293
Patch closure, n/N (%)	26/236 (11)	4/23 (17)	0.319

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide L/T ratio, lung-to-thorax transverse area ratio.
[a] $p < 0.05$.
[b] $p < 0.01$.

Table 4 Comparison of the parameters in the patients with ≥ 75% defects in the diaphragm

Development of pneumothorax	No (n = 99)	Yes (n = 26)	p
Gestational age (d), mean ± SD	262 ± 14	263 ± 14	0.828
Birth weight (g), mean ± SD	2625 ± 463	2779 ± 453	0.131
Apgar score at 1 min, median (interquartile range)	3 (2–5)	3 (2–4)	0.493
Caesarean section at delivery, n/N (%)	66 (67)	18 (69)	1.000
Prenatal diagnosis, n/N (%)	83 (84)	23 (88)	0.762
Liver-up, n/N (%)	38/77 (49)	9/23 (39)	0.478
L/T ratio < 0.08, n/N (%)	20/44 (45)	8/16 (50)	0.778
Use of HFOV, n/N (%)	82/95 (86)	24/26 (92)	0.521
Highest Pao_2 within 24 h after birth (Torr), mean ± SD	184 ± 128	195 ± 146	0.698
Lowest $Paco_2$ within 24 h after birth (Torr), mean ± SD	38 ± 18	36 ± 11	0.700
Best oxygenation index within 24 h after birth, mean ± SD	12.8 ± 13.3	15.6 ± 16.9	0.411
Mean airway pressure (cm H_2O), mean ± SD	14.3 ± 3.5	14.1 ± 2.6	0.834
Right-to-left shunting at ductus within 24 h after birth, n/N (%)	53/92 (58)	19/25 (76)	0.109
Use of iNO, n/N (%)	78/99 (79)	25/26 (96)	0.043[a]
Use of ECMO, n/N (%)	15/99 (15)	5/26 (19)	0.563
Time of surgery after birth (h), median (interquartile range)	69 (28–123)	100 (26–129)	0.893
Patch closure, n/N (%)	67/98 (68)	19/26 (73)	0.847

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; L/T ratio, lung-to-thorax transverse area ratio; SD, standard deviation
[a] $p < 0.05$.