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Un Nuevo Concepto en Medicina Perinatal

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**ORIGINAL ARTICLE** 

### Efficacy of double versus single phototherapy in treatment of neonatal jaundice: a meta-analysis

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#### Objetivo:

Evaluar la eficacia de la fototerapia doble en el manejo de la ictericia neonatal en comparación con la fototerapia única en lactantes con diferente peso al nacer y edad gestacional.

#### Método:

- Se realizaron búsquedas en diferentes fuentes: Cochrane, PubMed, Clinicaltrials.gov y literatura gris.
- Desde la fecha de inicio de estas bases de datos hasta agosto de 2019.
- El outcome primario fue la disminución de la bilirrubina sérica total (TSB) por hora.

- Método:
  - Criterios de elegibilidad:
    - Texto completo disponible
    - Recién nacidos solamente
    - Al menos un resultado informado para ser incluido en el metanálisis
    - Se debe informar tanto el ajuste de irradiancia como el ajuste de fototerapia
    - No haberse realizado exanguino transfusión antes de la intervención
    - Sin anomalías congénitas
    - Duración de la fototerapia de al menos 12 h

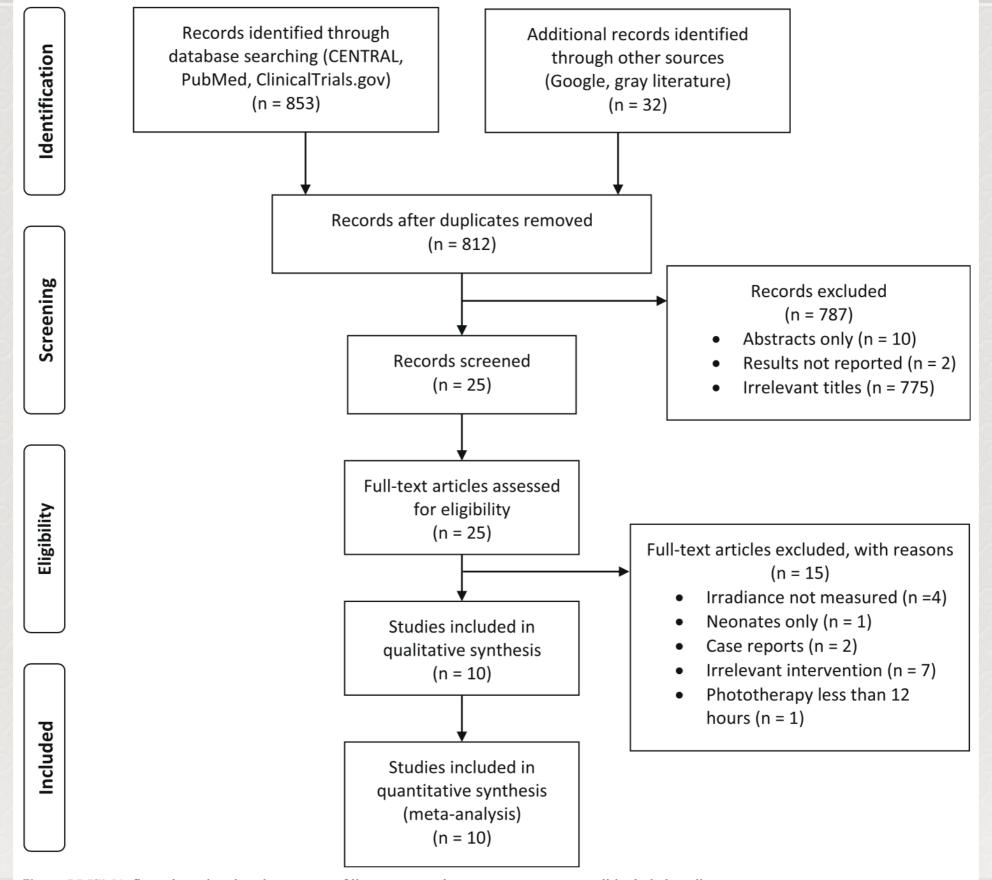


Fig. 1 PRISMA flow chart showing the process of literature search as percentages across all included studies

- Características de los estudios incluidos:
  - 6 eran ensayos controlados aleatorios, 3 eran ensayos controlados no aleatorios y solo 1 era un estudio de casos y controles (1104 pacientes incluidos).
  - Fototerapia doble:
    - cuatro estudios utilizaron almohadillas / mantas de fibra óptica
    - tres estudios utilizaron una configuración en la que había un solo panel junto con un panel de adición colocado en un ángulo diferente
    - un estudio usó un lecho fluido
    - otro estudio aumentó el número de lámparas y cambió de lámparas halógenas blancas a tubos fluorescentes azules.

 Table 1
 Characteristics of included studies

				Phototherapy setting			Irradiance setting		
Author	Study location	Study design	Total participants	Single	Double	Primary outcome	Single phototherapy	Double phototherapy	Results
Holtrop et al. [16], 1992	United States	Randomized controlled trial, single center	70, preterm, birth weight less than 2500 kg	2 machines, 1 with four white and four blue fluorescent lamps and other with six halogen lamps. Both were from above only	Single phototherapy method in addition with fiberoptic blanket	Decline of TSB per hour	Mean 9.2 μW/cm²/nm, mean 7 μW/cm²/nm	Mean 8.2 μW/cm <sup>2</sup> /nm	Decline of TSB per hour was significantly favorable towards the double phototherapy group.
Kang et al. [17], 1995	United States	Non-randomized controlled trial, single center	42, preterm, birth weight less than 2000 g	3 or 4 special blue and white lamps from above only	Single phototherapy method in addition with fiberoptic pad	TSB at 24 h, duration of phototherapy	7–9 μW/cm <sup>2</sup> /nm	$33-35 \mu W/cm^2/nm$	TSB at 24 h was significantly less and there was a significant reduction in duration of phototherapy in the double phototherapy
Garg et al. [18], 1995	Saudi Arabia	Randomized controlled trial, single center	50, preterm, term, birth weight more than 1500 g	4 blue fluorescent lamps from above only	Single phototherapy method in addition with fluid bed	Decline of TSB per hour, TSB at 24 h	7–8 μw/cm <sup>2</sup> /nm	$26-30 \mu W/cm^2/nm$	group. TSB at 24 h was significantly less and decline rate of TSB per hour was significantly greater in the double group.
Sarici et al. [19], 2000	Turkey	Non-randomized controlled trial, single center	100, term birth weight more than 2500 g	5 special blue lamps from above only	Single phototherapy method in addition with fiberoptic pad	Decline of TSB per hour, duration of phototherapy	18.4 μW/cm <sup>2</sup> /nm	28.5 μW/cm <sup>2</sup> /nm	Both decline of TSB per hour was greater and duration of phototherapy was less in the double phototherapy group. Both were not significant.
Boonyarittipong et al. [20], 2008	Thailand	Randomized controlled Trial, single center	60, term birth weight more than 2500 g	4 deep blue and two daylight florescent lamps above only	Single phototherapy method above in addition with four deep blue fluorescent lamps below	Decline of TSB per hour, TSB at 24 h	32.7 μW/cm²/nm from above.	33.7 $\mu$ W/cm <sup>2</sup> /nm from above and 32.6 $\mu$ W/cm <sup>2</sup> /nm from below.	Both TSB at 24 h and decline of TSB per hour were significantly favoring the double phototherapy group.
Silva et al. [21], 2009	Chile	Randomized controlled trial, single center	77, term birth weight more than 2500 g	6–8 fluorescent tubes from above only	Single phototherapy method in addition similar setting placed at 90°	Decline of TSB per hour	$\begin{array}{c} Mean \\ 9.4 \pm 1.94~\mu W/c - \\ m^2/nm \end{array}$	$\begin{array}{c} \text{Mean} \\ 11.7 \pm 0.72 \ \mu\text{W/c-} \\ \text{m}^2\text{/nm} \end{array}$	Decline of TSB per hour was favorable towards the double phototherapy group but not significantly.
Milyana et al. [22], 2011	Indonesia	Randomized controlled trial, single center	60, term birth weight more than 2500 g	5 compact fluorescent lamps from above only	5 compact fluorescent lamps from above and below	TSB at 24 h	$6.6 \mu W/cm^2/m$	$29.2~\mu W/cm^2/nm$	TSB at 24 h was less and had a significant difference in the double phototherapy group.
Al-Hafidh et al. [23], 2013	Iraq	Case control	191, preterm, term, birth weight more than 2500 g	3 white halogen lamps from above only	16 blue light fluorescent tubes from above only	Decline of TSB per hour	$10~\mu W/cm^2/nm$	$30~\mu\text{W/cm}^2\text{/nm}$	Decline of TSB per hour was significantly high in the double group.
Donneborg et al. [24], 2017	Denmark	Randomized controlled trial, single center	83, term birth weight more than 1800 g	Blue LED light from above only	Blue LED from above and fiberoptic blanket	TSB at 24 h	$66.5 \mu W/cm^2/nm$	65.2 μW/cm²/nm from above and 39.1 μW/cm²/nm from below	TSB at 24 h was less and had a significant difference in the

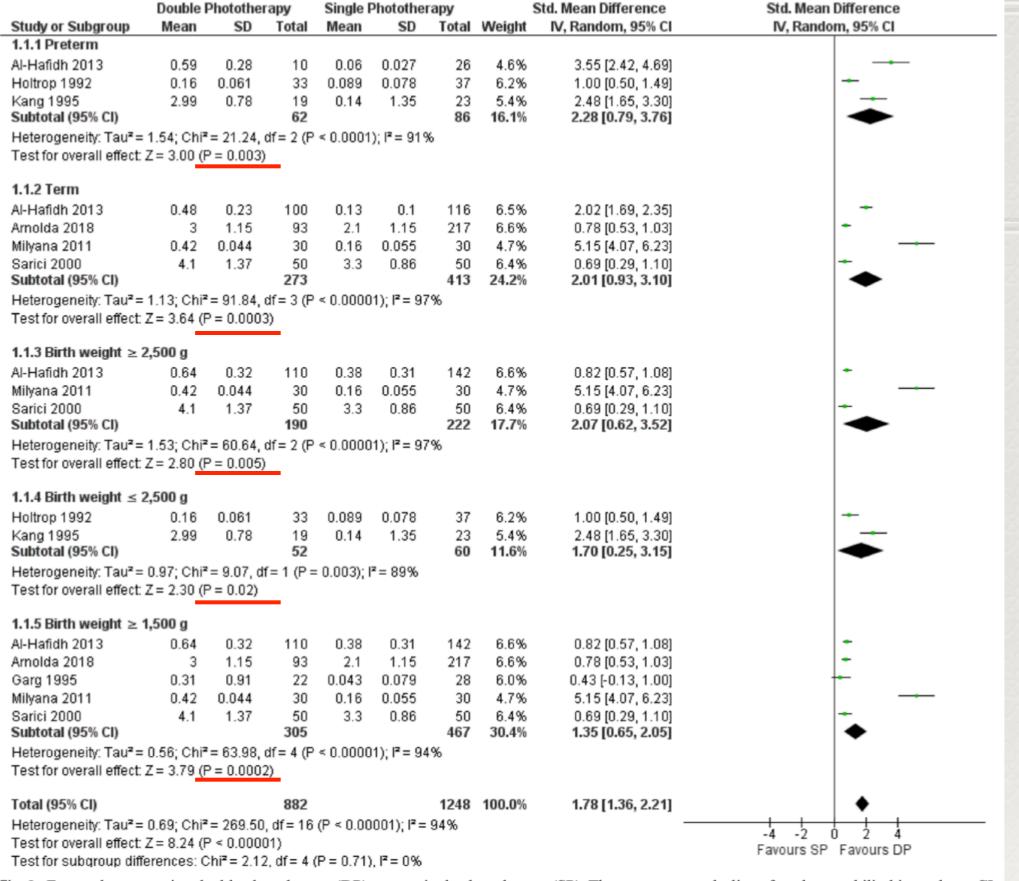


Fig. 2 Forest plot comparing double phototherapy (DP) versus single phototherapy (SP). The outcome was decline of total serum bilirubin per hour. CI, confidence interval: IV, inverse variance

Descenso de Bilirrubina por hora

7 estudios

#### Descenso de Bilirrubina en 24 h

#### 5 estudios

Study or Subgroup	Double P Mean [µmol/L]	hototherapy	Total M	Single P ean [µmol/L]	hototherapy	Total	Moight	Mean Difference IV, Random, 95% CI [µmol/L]	Voor	Mean Difference IV, Random, 95% CI [μmol/L]
1.2.1 Term	меан (µпол/с)	SD [pillol/L]	TOTAL IN	ean [µmor/L]	SD [pillol/L]	Total	vveigni	iv, Random, 95% Ci [pinoi/L]	real	iv, Kandom, 95% Ci [pinoi/L]
Boonyarittipong 2008	176	32.39	30	193	35.91	30	10.0%	-17.00 [-34.30, 0.30]	2008	-
Milyana 2011	127	27.36	30	235	31.46	30	10.1%	-108.00 [-122.92, -93.08]		-
Donneborg 2017 Subtotal (95% CI)	109	31.68	41 101	139	35.3	42 <b>102</b>	10.1% 30.2%	-30.00 [-44.42, -15.58] -51.75 [-107.81, 4.31]	2017	-
Heterogeneity: Tau <sup>2</sup> = 2	390.78; Chi <sup>2</sup> = 78.	52, df = 2 (P <	0.00001); (	z= 97%						
Test for overall effect: Z	= 1.81 (P = 0.07)	NT : :0								
		<ul> <li>No significa</li> </ul>	ativo							
1.2.2 Birth weight ≥ 2,5	_									
Boonyarittipong 2008	176	32.39	30	193	35.91	30	10.0%	-17.00 [-34.30, 0.30]		
Milyana 2011 Subtotal (95% CI)	127	27.36	30 <b>60</b>	235	31.46	30 <b>60</b>	10.1% 20.1%	-108.00 [-122.92, -93.08] -62.61 [-151.79, 26.57]		-
Heterogeneity: Tau² = 4	072 55: Chi² = 60	04 df = 1 /P =		z = 00%		00	20.170	-02.01[-151.75, 20.57]		
Test for overall effect: Z		.54, u1 = 1 (F \	0.00001),1	- 30 %						
restror overall ellect 2	- 1.50 (1 - 0.11)	<ul><li>No sig</li></ul>	nificativo							
1.2.3 Birth weight ≤ 2,5	500 g									
Kang 1995	106	18.8	19	173	32.5	23	10.1%	-67.00 [-82.74, -51.26]	1995	<u>+</u>
Subtotal (95% CI)			19			23	10.1%	-67.00 [-82.74, -51.26]		•
Heterogeneity: Not appl										
Test for overall effect: Z	= 8.34 (P < 0.000)	01)								
1.2.4 Birth weight ≥ 1,5	500 g									
Garg 1995	165	48.7	22	258	42.8	28	9.5%	-93.00 [-118.80, -67.20]	1995	
Boonyarittipong 2008	176	32.39	30	193	35.91	30	10.0%	-17.00 [-34.30, 0.30]	2008	
Milyana 2011	127	27.36	30	235	31.46	30	10.1%	-108.00 [-122.92, -93.08]		-
Donneborg 2017 Subtotal (95% CI)	109	31.68	41 123	139	35.3	42 130	10.1% <b>39.7</b> %	-30.00 [-44.42, -15.58] - <b>61.70 [-107.96, -15.43]</b>		•
Heterogeneity: Tau² = 2	138.81; Chi <sup>2</sup> = 86.	.25, df = 3 (P <	0.00001); (	²= 97%						
Test for overall effect: Z	= 2.61 (P = 0.009)	)								
Total (95% CI)			303			315	100.0%	-59.42 [-85.32, -33.52]		•
Heterogeneity: Tau <sup>2</sup> = 1	671.11; Chi <sup>2</sup> = 23	0.73, df = 9 (P	< 0.00001);	I <sup>2</sup> = 96%				•		200 400
Test for overall effect: Z			,							-200 -100 0 100 Favours DP Favours SP
Test for subgroup differ	ences: Chi2 = 0.30	0, df = 3 (P = 0)	.96), I²= 0%	,						ravouis Dr. ravouis Sr

Fig. 3 Forest plot comparing double phototherapy (DP) versus single phototherapy (SP). The outcome was total serum bilirubin ( $\mu$ mol/L) levels at 24 h. CI, confidence interval; IV, inverse variance

- Duración de la fototerapia: 3 estudios
  - \* subgrupo de prematuro y peso al nacer  $\leq$  2500 g (1): hubo un resultado significativo a favor de la fototerapia doble. ( $p \leq$  0.001).
  - subgrupos de término y peso al nacer  $\geq$  1500 g (2): favorecieron significativamente la fototerapia doble para reducir la duración de la fototerapia. (p = <0.001).
  - El tamaño total del efecto global favoreció significativamente hacia la fototerapia doble que la fototerapia simple (p≤0.001).
- Estancia hospitalaria: 2 estudios
  - El análisis agrupado mostró que la fototerapia doble favoreció significativamente en la reducción de la estadía hospitalaria que la fototerapia simple (p≤0.001).

### Conclusiones:

- La fototerapia doble es superior a la fototerapia simple, ya que logra una disminución más rápida de TSB por hora y niveles más bajos de TSB a las 24 h del inicio de la fototerapia.
- Los futuros ensayos controlados aleatorios multicéntricos pueden evaluar los efectos adversos de la fototerapia doble con respecto a la edad gestacional y el peso al nacer de los lactantes para obtener una evidencia clínica más favorable.

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#### **ORIGINAL ARTICLE**



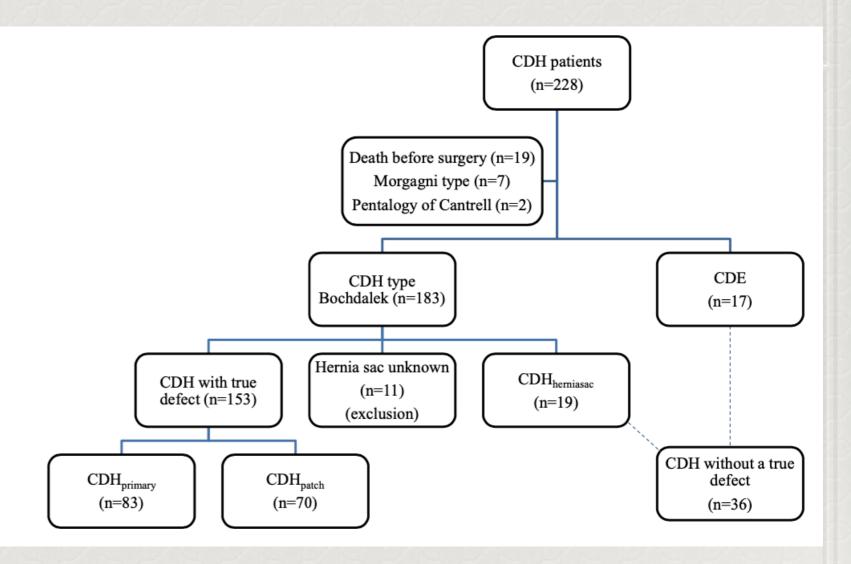
### Congenital diaphragmatic eventration and hernia sac compared to CDH with true defects: a retrospective cohort study

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- Ll tipo más común de defecto diafragmático es un defecto posterolateral también conocido como hernia de Bochdalek, que representa aproximadamente el 85% de los casos
- \* Eventración diafragmática congénita (CDE)
- Los pacientes con CDH tipo Bochdalek pueden tener un defecto verdadero ("clásico") o un saco herniario, que se ha descrito en 14-20% de los casos.
- Objetivo:
  - Evaluar si existe una diferencia en el resultado clínico entre Bochdalek CDH con un defecto verdadero y pacientes sin un defecto verdadero (pacientes con saco herniario y eventración).
  - Se realizará un subanálisis para evaluar si la presencia de un saco herniario tiene resultados clínicos más comparables con el CDE en lugar del CDH tipo Bochdalek con un defecto verdadero.

- Métodos: Estudio retrospectivo de cohorte
  - Criterios de inclusión:
    - Todos los pacientes reparados quirúrgicamente con un CDH diagnosticado entre enero de 2000 y diciembre de 2016 en un centro de alto volumen (Radboudumc-Amalia Children 's hospital, Nijmegen, Países Bajos)
  - Criterios de exlusión:
    - Datos incompletos (sin información sobre el tipo de defecto y la presencia de saco herniario)
    - Hernias de Morgagni y pentalogía de Cantrell
    - Se excluyeron los pacientes que murieron antes de la reparación quirúrgica, porque no había información disponible sobre el tipo de defecto.
    - Para los resultados pulmonares a largo plazo a los 30 días o al alta, los pacientes que murieron antes de esta fecha fueron excluidos en los análisis.

**Fig. 1** Exclusion and division of subgroups of the total group of CDH patients



- Outcome
  - Primario: la supervivencia y la tasa de recurrencia en el 1er año de vida
  - Secundario:
    - tratamiento médico y quirúrgico (ECMO, reparación primaria o parche)
    - complicaciones quirúrgicas perioperatorias
    - necesidad de suplementos de oxígeno a los 30 días de vida y la necesidad de suplementos de oxígeno al momento del alta a su hogar u otro hospital.

#### 200 pacientes elegibles

Table 1 Demographics and perinatal characteristics of CDH with true defect, CDE, and CDH<sub>hernia sac</sub>

	CDE $(n = 17)^{9\%}$	$CDH_{herniasac}$ $(n = 19)$	$CDH_{\text{truedefect}} (n = 153)$	P value	P value (CDE/CDH <sub>herniasac</sub> )
Gender – female	9 (52.9)	10 (52.6)	52 (34)	0.11	0.99
Gestational age in weeks <sup>1</sup> , median (range)	38.1 (31.3–41.7)	38.3 (30.1–42.7)	38.3 (27.7–42.3)	0.85	0.91
Birth weight in grams <sup>1</sup> ,	2793 (817)	2997 (859)	3004 (609)	0.55	0.52
Mean (SD)					
Liver up	9 (52.9)	9 (47.4)	46 (30)	0.06	0.74
Apgar score <sup>3</sup> , median (range)					
1 min	8 (1–10)	8 (3–9)	6 (0–9)	0.13	0.87
5 min	9 (3–10)	9 (7–10)	8 (1–10)	0.06	0.51
Side hernia				0.008	0.28
Left	10 (58.8)	14 (73.7)	131 (85.6)		
Right	5 (29.4)	5 (26.3)	20 (13.1)		
Bilateral	2 (11.8)	0 (0)	2 (1.3)		

Missing: 14, 35

CDE congenital diaphragmatic eventration; CDH<sub>hernia sac</sub> congenital diaphragmatic hernia, Bochdalek type, with hernia sac; CDH congenital diaphragmatic hernia

Defecto del lado derecho fue más frecuente en en CDE y CDH saco herniario CDE y CDH saco herniario: más defectos genéticos (31 y 26%)

Table 2 Treatment and outcomes of CDH with true defect, CDE, and CDH<sub>hemia sac</sub>

	CDE $(n = 17)$	$CDH_{hemiasac}$ (n = 19)	$CDH_{truedefect}$ ( $n = 153$ )	P value	P value (CDE/CDH <sub>herniasac</sub> )
Treatment					
Medical					
Pulmonary hypertension <sup>1</sup>	7 (43.8)	7 (41.2)	75 (56)	0.37	0.88
Use of inhaled nitric oxide <sup>2</sup>	3 (20)	6 (31.6)	67 (45.3)	0.11	0.70
ECMO	3 (17.6)	2 (10.5)	59 (38.6)	0.02	0.65
Surgical					
Method of repair				0.02	0.65
Primary	14 (82.4)	17 (89.5)	83 (54.2)		
Patch	3 (19)	2 (10.5)	70 (45.8)		
Non-closure of fascia <sup>1</sup>	1 (6.7)	1 (5.6)	41 (27.7)	0.03	1.00
Outcome					
Survival					
30-days	17 (100)	19 (100)	126 (82.4)	0.03	_
1-year	16 (94.1)	19 (100)	116 (75.8)	0.01	0.47
Surgical complications	6 (35.3)	5 (26)	53 (34.9)	0.76	0.72
Hemorrhage <sup>3</sup>	2 (12.5)	1 (5.3)	16 (84.2)	0.73	0.58
Chylothorax <sup>3</sup>	1 (6.3)	2 (10.5)	30 (19.7)	0.28	1.00
Recurrence of hernia					
30 days	1 (5.9)	2 (10.5)	0 (0)	<0.001	1.00
1 year <sup>3</sup>	2 (11.8)	3 (16.7)	7 (4.7)	0.10	1.00

Missing: 13, 22, 31

CDE congenital diaphragmatic eventration; CDH<sub>herniasac</sub> congenital diaphragmatic hernia, Bochdalek type, with hernia sac; CDH<sub>truefefect</sub> congenital diaphragmatic hernia, Bochdalek group, without hernia sac; ECMO extracorporeal membrane oxygenation; NICU neonatal intensive care unit

 Table 3
 Demographics and perinatal characteristics of CDH patients with and without a true defect

	$CDH_{notruedefect}$ ( $n = 36$ )	$CDH_{truedefect}$ ( $n = 153$ )	P value
Gender – female	19 (52.8)	52 (34)	0.04
Gestational age in weeks <sup>1</sup> , median (range)	38.3 (30.1–42.7)	38.3 (27.7–42.3)	0.64
Birth weight in grams <sup>2</sup> , mean (SD)	2911 (834)	3004 (609)	0.48
Liver up <sup>4</sup>	18 (50)	46 (30)	0.02
Apgar score <sup>6</sup> , median (range)			
1 min	8 (1–10)	6 (0–9)	0.05
5 min	9 (3–10)	8 (1–10)	0.02
Side hernia			0.02
Left	24 (66.7)	131 (85.6)	
Right	10 (27.8)	20 (13.1)	
Bilateral	2 (5.6)	2 (1.3)	
Major cardiac malformations <sup>7</sup>	0 (0)	3 (2)	1.00
Chromosomal anomalies <sup>8</sup>	4 (11.4)	9 (6)	0.28
Other birth defects <sup>7</sup>	10 (28.6)	16 (10.5)	0.01

Missing: 127, 223, 313, 41, 58, 633, 72, 85

 $CDH_{notruedefect}$  eventration and hernia sac patients;  $CDH_{truefefect}$  congenital diaphragmatic hernia, Bochdalek group, without hernia sac; CDH congenital diaphragmatic hernia

Table 4 Treatment and surgical outcomes of CDH patients with and without a true defect

	$CDE_{notrue defect}$ ( $n = 36$ )	$CDH_{truedefect}$ ( $n = 153$ )	P value
Treatment			
Pulmonary hypertension <sup>1</sup>	14 (42.4)	75 (56)	0.16
Use of inhaled nitric oxide <sup>2</sup>	9 (26.5)	67 (45.3)	0.04
ECMO	5 (13.9)	59 (38.6)	0.005
Non-closure of fascia <sup>3</sup>	2 (6.1)	41 (27.7)	0.08
Abdominal patch	1 (2.8)	27 (17.6)	0.02
Outcome			
Survival			
30-days	36 (100)	126 (82.4)	0.002
1-year	35 (97.2)	116 (75.8)	0.006
Surgical complications <sup>4</sup>	11 (30.6)	53 (34.9)	0.62
Hemorrhage <sup>5</sup>	3 (8.6)	16 (10.5)	1.00
Chylothorax <sup>5</sup>	3 (8.6)	30 (19.7)	0.12
Recurrence of hernia			
30 days	3 (8.3)	0 (0)	0.006
1 year <sup>6</sup>	5 (14.3)	7 (4.7)	0.05

Missing: 122, 27, 38, 41, 52, 66,

 $CDH_{notrue defect}$  eventration and hernia sac patients;  $CDH_{true fefect}$  congenital diaphragmatic hernia, Bochdalek group, without hernia sac; ECMO extra-corporeal membrane oxygenation; NICU neonatal intensive care unit

Tratamiento Qx: CDH no verdadero tuvieron cierre primario 94% comparado con 72% de CDH (p 0,02)

Table 5 Treatment and outcomes of CDH<sub>notruefect</sub> versus CDH<sub>Bprim</sub> and CDH<sub>notruedefect</sub> versus CDH<sub>patch</sub>

	$CDH_{notruedefect}$ ( $n = 36$ )	$CDH_{prim} (n = 83)$	P value	$CDH_{patch}$ (n = 70)	P value
Treatment					
Pulmonary hypertension	14 (42.2) <sup>1</sup>	24 (32.4) <sup>2</sup>	0.32	51 (85) <sup>3</sup>	< 0.001
Use of inhaled nitric oxide	9 (26.5) <sup>4</sup>	21 (26.3) <sup>1</sup>	0.98	46 (68) <sup>4</sup>	< 0.001
ECMO	5 (13.9)	12 (14.5)	0.94	47 (67)	< 0.001
Non-closure of fascia	2 (6.11	$10(12.3)^4$	0.50	31 (46) <sup>1</sup>	< 0.001
Abdominal patch	1 (2.8)	3 (3.6)	1.00	24 (34)	< 0.001
Outcome					
Survival					
1-year	35 (97.2)	79 (95.2)	1.00	37 (52.9)	< 0.001
Surgical complications	11 (30.6)	17 (21) <sup>5</sup>	0.34	37 (52.9)	0.03
Hemorrhage	3 (8.6) <sup>5</sup>	3 (3.7) <sup>5</sup>	0.36	13 (18.6)	0.18
Chylothorax	3 (8.6) <sup>5</sup>	$10(12.2)^5$	0.75	20 (28.6)	0.02
Recurrence of hernia					
30 days	3 (8.3)	0 (0)	0.03	0 (0)	0.04
1 year	$5(14.3)^5$	$1(1.2)^5$	0.009	6 (9.1) <sup>6</sup>	0.51
Pulmonary state 30 days					
O <sub>2</sub> supplement	15 (45.5) <sup>1</sup>	6 (8) <sup>7</sup>	<0.001	24 (60) <sup>8</sup>	0.22
Mechanical ventilator support	14 (42.4) <sup>1</sup>	5 (6.7) <sup>7</sup>	<0.001	18 (45) <sup>8</sup>	1.00
Pulmonary state discharge					
O <sub>2</sub> supplement	8 (24.2) <sup>1</sup>	4 (5) <sup>7</sup>	0.01	8 (24.2) <sup>9</sup>	1.00
Mechanical ventilator support	$6(18.2)^1$	$0(0)^7$	0.01	4 (12.1) <sup>9</sup>	0.73

Missing: 13, 29, 310, 42, 51, 64, 78, 830, 937

 $CDH_{notruedefect}$  eventration and hernia sac patients;  $CDH_{prim}$  congenital diaphragmatic hernia, Bochdalek group, without hernia sac, primary repair;  $CDH_{patch}$  congenital diaphragmatic hernia, Bochdalek group, without hernia sac, patch repair; ECMO extracorporeal membrane oxygenation; NICU neonatal intensive care unit

#### Conclusiones

- La tasa de recurrencia para pacientes sin un verdadero defecto de HDC parece ser más alta.
- Las similitudes en estos pacientes sin un defecto verdadero, encontrado en este estudio pueden ser una indicación de que estos defectos a menudo se subestiman.
- Los resultados a corto plazo de estos pacientes son comparables a los pacientes con un defecto diafragmático verdadero pequeño, mientras que el pronóstico a largo plazo es más comparable a los pacientes con un defecto grande.
- Se necesitan más estudios para evaluar si las técnicas quirúrgicas (para usar o parchear o no) para estos defectos específicos deben ajustarse para prevenir las recurrencias y mejorar el resultado pulmonar a los 30 días de edad y al alta.