

# Optimal early surgery timing for congenital diaphragmatic hernia: A systematic review

Hery Poerwosusanta, PhD<sup>1</sup>, Donny Aditia, MD<sup>2</sup>, Gunadi, PhD<sup>2</sup>, Pricilia Gunawan Halim, MD<sup>3</sup>, Mutia Juliana, MD<sup>4</sup>

<sup>1</sup>Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia, <sup>2</sup>Pediatric Surgery Division, Department of Surgery, Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital, Yogyakarta, Indonesia, <sup>3</sup>Department of Pediatric, Faculty of Medicine, Lambung Mangkurat University/Ulin Hospital, Banjarmasin Indonesia, <sup>4</sup>Institute Kesehatan Imanuel, Bandung, Indonesia

## ABSTRACT

**Introduction:** Congenital diaphragmatic hernia (CDH) is a failure of closure of the pleuro-peritoneal canal due to faulty embryogenesis caused herniation of intra-abdominal contents into the chest. There needs to be more clarity about the optimal surgical timing for CDH. The aim of this study is to determine the optimal surgical timing for CDH using a systematic review analysis.

**Materials and Methods:** Our study used the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020. The literature search approach used publications between 2013 and 2023 using Pubmed and SagePub databases. Studies were included if they contained reports of the best timing for emergency surgery for CDH repair. We did not include review articles and unpublished data.

**Results:** Five articles met the criteria. The overall result, the first pre-operative 24-hour oxygenation index mean, was temporally reliable and representative (intraclass correlation coefficient = 0.70, 95% CI = 0.61–0.77). Within any severity level, there were no differences in 90-day survival or mortality rate between delayed repair and early repair ( $p = 0.002$ ). As a result, there is no optimal timing for surgery in severe cases of CDH. A delay in repair did not predict an increased risk of death, nor did it suggest an increased need for post-operative extracorporeal membrane oxygen therapy.

**Conclusion:** Regardless of the severity of the illness, the timing of CDH repair does not affect the mortality rate. Surgery is done after the physiology index achievement.

## KEYWORDS:

*Congenital abnormality; congenital hernia diaphragmatic; emergency surgery*

## INTRODUCTION

Congenital diaphragmatic hernia (CDH) is herniation of intra-abdominal contents into the chest as a result of faulty embryogenesis and due to failure of closure of the pleuro-peritoneal canal. The right pleuro-peritoneal canal closes faster than the left in intrauterine, resulting in a left-side

posterolateral defect (Bochdalek's hernia, 75%). The rest of CDH may occur on the right side, central defect, congenital absence of diaphragm or anterior (Morgagni hernia).<sup>1,2</sup> Embryopathy and mechanical compression factors from diaphragm muscle abnormalities cause the triad of pulmonary hypoplasia, pulmonary hypertension and cardiac dysfunction with overall survival of 50%.<sup>3</sup> Closure of the pleuroperitoneal tract has not yet occurred by the time the midgut returns to the abdomen during the 9th and 10th weeks of gestation.<sup>4</sup> This congenital anomaly occurs in 1 in 2400–5000 births, with a 2:1 male-to-female ratio and a 5:1 left-to-right diaphragm hernia ratio and 40–50% die. Permissive hypercapnia and delayed surgery repair improved survival rates to over 75%.<sup>5,6</sup> The cause of CDH is unknown, suggesting that CDH may be caused by exposure to genetic predisposition and susceptibility to environmental factors. The CDH impact on lung development and function has been well established.<sup>7</sup>

Pulmonary hypoplasia and reactive pulmonary hypertension are CDH newborns' respiratory problems. The most severely impacted neonates exhibited respiratory difficulty at delivery and respiratory symptoms within 24 hours. Asymmetrical scaphoid abdomen and bulging chest are characterised in newborns.<sup>5,6</sup> Some researchers wait until the infant has released mechanical ventilation and needs a lower ventilator setting before surgery. In contrast, others follow the severity of pulmonary hypertension with serial echocardiographic examinations and wait until it stabilises.<sup>7</sup> There are no practice or simple clinical indicators to determine the surgery's optimal time.

Infants predicted to have good lung development (good lung growth on an antenatal scan, left-sided defect and no liver involvement) should be considered for the non-intubation breathing trial. Early echocardiography shows the degree of cardiac and coexisting defects, pulmonary hypertension and the right-to-left shunt for a medical management guide.<sup>8–12</sup> This study aims to determine simple clinical criteria for the best time for emergency surgery in a CDH.

## MATERIALS AND METHODS

### Protocol

By following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 rules, these

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Corresponding Author: Hery Poerwosusanta

Email: herpoerwo@ulm.ac.id

Table I: The literature included in this study

Author	Origin	Method	Sample Size	Result
Cox <sup>13</sup>	United States of America (USA)	Retrospective cohort study	158 neonates	OI readings are stabilised over time and change very little after 24 hours. When surgical repair of CDH is put off past the point of initial stability, the number of days on a ventilator and the age at which the patient is released goes up without any improvement.
Yamoto <sup>14</sup>	Japan	Prospective cohort study	276 patients with isolated left-sided CDH	The study indicates that surgery should not be performed within 24 hours of birth for patients whose CDH is of moderate severity, that there is no benefit to delaying surgery for more than 72 hours in patients whose CDH is of mild severity, and that there is no definitive optimal time to perform surgery in severe cases of CDH. These findings suggest no optimal time to perform surgery in severe cases of CDH.
Deeney <sup>15</sup>	United States of America (USA)	Retrospective cohort study	77 neonatal patients with Bochdalek hernias	Implementing pulmonary arterial pressure of 80% of systemic pressure in echocardiogram as a non-invasive method before CDH repair may reduce acute post-operative decompensation. There were no differences existed in longer-term survival.
Okuyama <sup>16</sup>	Japan	Prospective cohort study	477 neonates with isolated CDH	It does not appear that the timing of CDH repair impacts 90-day survival, regardless of the severity of the condition. Patients whose injuries are of a moderate degree may benefit from early repair because it shortens the duration of treatment.
Hollinger <sup>17</sup>	United States of America (USA)	Prospective cohort study	1,385 CDH Registry infants without pre-operative extracorporeal membrane oxygen therapy (ECMO)	When considering all known risk variables, the timing of CDH repair in low-risk newborns does not appear to affect mortality. Nevertheless, the clinical factors that guide the time of elective CDH repair continue to be unknown.

authors ensured it met the requirements. This protocol provides that the conclusions of the inquiry are accurate.

#### Criteria for Eligibility

In this literature review, we investigate the best timing for emergency surgery for CHD repair to demonstrate the relevance of the difficulties of the criteria of optimal early surgery.

The researchers needed to fulfil the following requirements: 1) The papers were written in English, and the best time for emergency surgery for CHD was determined. The published manuscript must meet both criteria. 2) The studies published after 2013 and before this systematic review are deemed relevant. The studies were not permitted to include editorials, did not have a DOI, published review articles and were identical to published papers.

#### Search Strategy

We used "congenital hernia diaphragmatic bochdalek"; "optimal timing of surgery"; "baby/neonate"; "neonatal/baby mortality" and "prediction factor" as keywords. The studies search in the systematic review was carried out from July, 11<sup>th</sup>2023 using the PubMed and SagePub databases by inputting the words: "congenital OR "congenitally" AND "bochdalek" OR "bochdaleks" AND "hernia, diaphragmatic OR "hernia" AND "diaphragmatic" OR "diaphragmatic hernia" OR "diaphragmatic AND "hernia" AND "optimal" OR "optimality" OR "optimally" OR "optimisation" OR "optimisations" OR "optimise"

OR "optimised" OR "optimiser" OR "optimisers" OR "optimises" OR "optimising" AND "timely" OR "timing" OR "timings" AND "surgery" OR "surgical procedures, operative" OR "surgical" AND "procedures" AND "operative" OR "operative surgical procedures" OR "general surgery" OR "general" AND OR "general surgery" OR "surgery s" OR "surgerys" OR "surgeries" AND "baby neonate" AND "neonatal baby" AND "mortality" OR "mortalities" OR "mortality" AND "predict" OR "predictabilities" OR "predictability" OR "predictable" OR "predictably" OR "predicted" OR "predicting" OR "prediction" OR "predictions" OR "predictive" OR "predictively" OR "predictiveness" OR "predictives" OR "predictivities" OR "predictivity" OR "predicts" AND "factor" OR "factor s" OR "factors" AND y\_10 AND clinicaltrial used in searching the literature.

#### Data Retrieval

After reading each study's abstract and title, the writers examined and determined whether the study satisfied the inclusion criteria. The writers decided which previous research was selected for the article source. This conclusion was drawn after looking at many studies with the same no. All submissions must be written in English and cannot be seen elsewhere.

Only those papers that satisfied all inclusion criteria were considered for the systematic review, reducing the number of results to only those pertinent to the search. We do not assume any study's conclusions that do not satisfy our requirements. After this, the research findings will be analysed in great detail. The following pieces of information

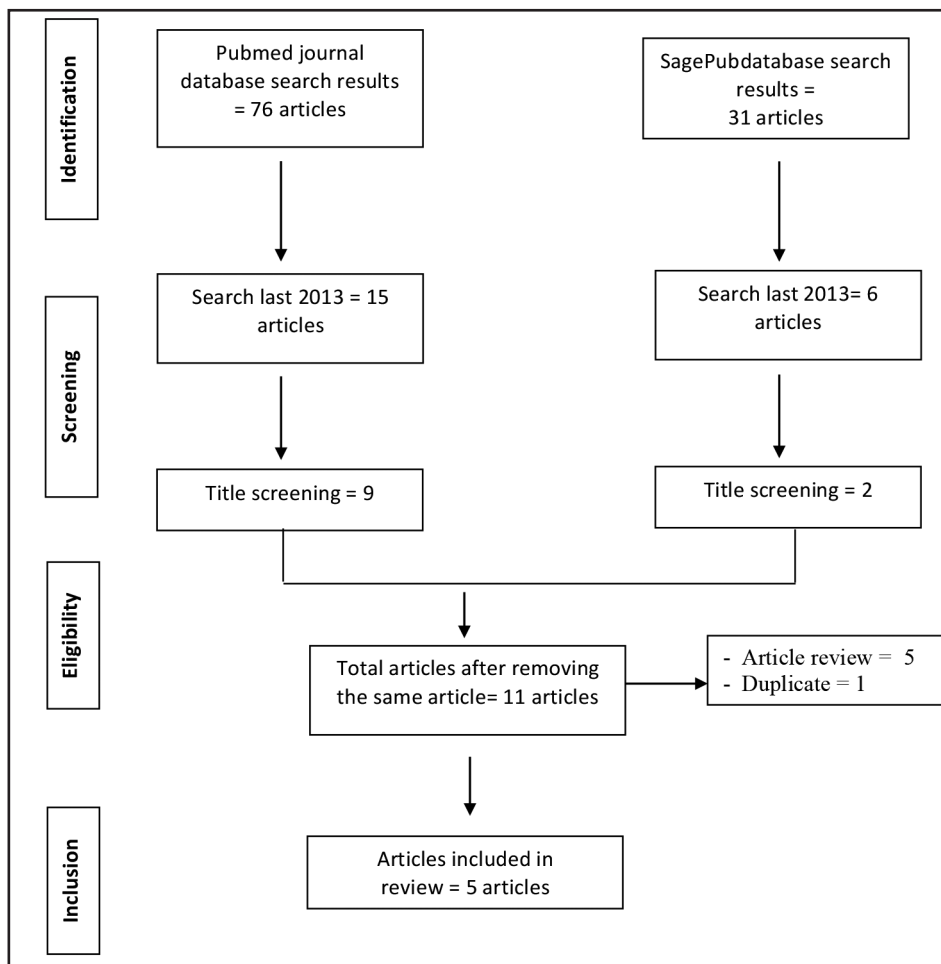


Fig. 1: Article search flowchart

were uncovered due to the inquiry that was carried out for this study: names, authors, publication dates, location, study activities and parameters.

*Quality Assessment and Data Synthesis*

Each author studied the research in the publication's title and abstract before deciding which journals to explore further. The next step will be to evaluate all of the articles suitable for inclusion in the review because they match the criteria set forth for that purpose. After that, we will determine which articles to include in the study depending on the findings that we have uncovered. These criteria are utilised in selecting papers for further assessment to simplify the process of selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review are being discussed (Figure 1).

**RESULTS**

In the PubMed database, our search results included 76 articles, whereas on SagePub, 31 articles. The search results for the 2013 last year PubMed were 15 articles and six articles for SagePub. In the end, we compiled 11 papers, 9 of which came from PubMed and 2 from SagePub. We included five research that met the criteria.

Cox et al.<sup>13</sup> showed the first 24 h oxygenation index (OI) pre-operative mean was temporally reliable and representative (intraclass correlation coefficient (ICC) = 0.70, 95% CI = 0.61–0.77). A pre-operative OI of ≤ 9.4 (AUC = 0.95) predicted survival. An increased ventilator day (1.4, 95% CI = 1.1–1.9) and discharge age (1.5, 95% CI = 1.2–2.0) after the surgical delay in OI ≤ 9.4. When prospectively cohort, an OI ≤ 9.4 reflected pre-operative physiologic stability. OI stabilises by 48 h, and delayed repair (DR) beyond OI ≤ 9.4 may be associated with a more prolonged ventilator and hospital course without a survival benefit.

Yamoto et al.<sup>14</sup> repaired in 24–47 h had a decreased death rate compared to the other groups. There were no statistically significant variations in fatality rates between the four groups for moderate or severe cases. G2 dramatically enhanced survival rates in mild cases, compared to G1 (<24 h), leading to a better overall outcome. Multivariate analyses showed that G2 had a lower mortality rate than the other groups. There were no significant differences in mortality across the four groups in mild and severe cases.

Deeney et al.<sup>15</sup> showed groups with comparable initial characteristics. In group 2 (repaired CHD after echocardiogram-estimated pulmonary artery pressure ≤80% systemic blood pressure specific criteria implementation), post-operative decompensation occurred less frequently than in group 1 (corrected after protocol implementation) (17% vs

48%,  $p < 0.01$ ). Similar results were obtained after adjusting for repair type, hepatic herniation and prematurity (15% vs 37%,  $p = 0.04$ ). 94% of Group 2 patients survived 30 days after surgery, compared to 80% of Group 1 patients ( $p = 0.06$ ).

Okuyama et al.<sup>16</sup> showed that 90-day survival differed considerably between the three severity levels ("mild" = 97%, "moderate" = 89% and "severe" = 76%,  $p = 0.002$ ), there were no variations in 90-day survival between DR and early repair (ER) within any severity level. There were no changes in treatment time between ER and DR in the "mild" condition. Treatment duration in the "moderate" category was shorter in the ER than in the DR (ventilation 11 vs 16 days, oxygen 15 vs 20 days and hospitalisation 34 vs 48 days). Treatment time in "severe" was shorter in ER than in DR, whereas the best OI was higher in DR than in ER.

Hollinger et al.<sup>17</sup> showed the unadjusted odds ratio (OR) for death increased considerably with DR (group 2 [4–7 days] = 1.73 [95% CI = 1.00–2.98]; group >8 = 3.42 [95% CI = 1.97–5.96]). Group 2 had an OR = 1.73 and Group 3 had an OR = 3.42. Both of these ratios were significantly higher than 1. However, when the severity of the disease was taken into account, a delay in repair did not predict an increased risk of mortality (group 2 = 1.2 [95% CI = 0.7–2.2]; group 3 = 1.4 [95% CI, 0.8–2.6]), nor did it foreshadow a higher requirement for post-operative extracorporeal membrane oxygen therapy (ECMO) (group 2 = 1.1 [95% CI = 0.5–2.4]; group 3 = 0.5 [95% CI = 0.2–1.4]).

## DISCUSSION

CDH is a physiological emergency, not a surgical one. Maintaining cardiorespiratory stability is very important. Irreversible pulmonary hypoplasia and potentially reversible pulmonary hypertension cause infant CDH-related respiratory problems. The balance between these two factors determines the response to therapy. It is ultimately manifested by increased pulmonary vascular resistance and pulmonary artery pressure, right-to-left shunts in the ducts and foramen and progressive hypoxemia. No current proven therapy to increase lung growth exists, so therapeutic interventions aim to manage pulmonary vascular tone.<sup>7,11</sup>

Reviewing the pertinent surgical factors: the side and position of the lesion, the prediction organ size and the degree of hepatic herniation (if present, is essential). The CDH will touch the chest and abdominal cavity organs. The diaphragm hole is patched or closed using either primary repair. Both open or thoracoscopic approaches can be used during surgery.<sup>18</sup>

Nonetheless, the precise definition or criteria for the optimal timing of the surgery are unknown. Due to the heterogeneity of CDH disease severity, some patients can tolerate an ER, whereas others require a period of stabilisation before the appropriate operation can be performed securely. Given the lack of published studies addressing this issue, it was evident that a randomised controlled trial, multivariate analysis, or stratified analysis would be required to determine the optimal timing of surgery for this condition.<sup>16</sup>

Several conditions must be considered when carrying out a CDH repair, including (1) Echocardiographic evidence of pulmonary pressures below 80% systemic; (2) NICU bedside

repair until pulmonary pressures are <50% systemic; (3) Repair of severe cases on ECMO within 72 hours once coagulation status is stable. 24-hour pre-repair aminocaproic acid; (4) Mild or moderate cases requiring ECMO: repair following decannulation; (5) A transversus abdominus muscle flap is best for patching left-sided CDH. Prosthetic patches can treat right-sided CDH; (6) Without ECMO repair, no chest tube will be implanted during surgery; (7) Expect a pleural effusion on the operative side and watch for tension and breathing problems; (8) Some CDH patients will develop a postsurgical chylothorax that requires drainage and octreotide. Albumin must replace significant drainage and (9) Monitor immunoglobulins (IgG) weekly if there is considerable drainage and provide intravenous IgG if <200 mg/dL.<sup>15,19–21</sup>

Surgical emergency is the treatment of CDH, and the prognosis depends on the degree of pulmonary hypoplasia. There is much debate and minimal criteria regarding the optimal timing of surgery. The CDH EURO Consortium recommendation of the state that the following physiological parameters before surgery: normal mean arterial pressure for gestation, preductal oxygen saturation consistently 85–95% on FiO<sub>2</sub> <0.5, lactate below 3 mmol/L and urine output more than 1 ml/kg/h.<sup>12,22</sup>

Currently, cardiopulmonary stabilisation is followed by definitive surgical repair to treat CDH. The paradigm transition from emergent to DR occurred in 1987 when Sakai and colleagues demonstrated that respiratory system compliance frequently deteriorates after CDH repair.<sup>10,23</sup> The study showed that CDH repair at 24–47 h (early) after birth has the lowest mortality rate. CDH repair at 48–71 h results in less vasodilator medication use and fewer intraoperative complications. In contrast, CDH repair occurring more than 72 hours after birth is associated with numerous chronic pulmonary diseases and longer hospital stays.<sup>16,17,24</sup>

There was no significant difference in longer-term secondary outcomes, such as survival to discharge, when a protocol was implemented that required an echocardiogram-estimated pulmonary arterial pressure of 80% of systemic pressure before CDH repair. This protocol may reduce the incidence of acute post-operative decompensation, but there was no difference in the longer-term secondary outcomes. There is also evidence of a trend for improved 30-day post-operative survival, which did not reach statistical significance.<sup>15</sup>

The first 24-hour OI was temporally reliable and representative of the pre-operative mean (ICC = 0.70, 95% CI = 0.61–0.77). A pre-operative OI of  $\leq 9.4$  (AUC = 0.95) predicted survival. An increased ventilator day (1.4, 95% CI = 1.1–1.9) and discharge age (1.5, 95% CI = 1.2–2.0) in surgical delay after an OI  $\leq 9.4$ . An OI  $\leq 9.4$  was reflected in physiologic stability before repair. OI stabilises by 48 h, and DR beyond OI  $\leq 9.4$  may be associated with a more prolonged ventilator and hospital course without a survival benefit.<sup>13</sup>

The most common way to decide when to fix a CDH is to wait for an unspecified amount of time until the surgeon thinks the patient is "stable" enough. The vague term usually means the patient is stable on the ventilator, has optimal blood flow with minimal pressure support and has little extrapulmonary right-to-left shunting. Previous studies that looked at the effect

of waiting to fix a CDH did not find a difference in life rates between those who got the problem fixed right after birth and those who did not.<sup>15,19</sup>

The other CDH prediction factors are pre-natal imaging by ultrasound and MRI, and post-natal factors include birth weight, Apgar score, arterial blood gas, OI, defect size, other severe congenital anomalies, oxygen saturation, vital signs and need for medication.<sup>3,14</sup> Pre-natal imaging usually measures the lung-to-head ratio (LHR), the observed/expected LHR (O/E-LHR), the observed/expected total fetal lung volume (O/E-TFLV), absolute fetal lung volume (FLV), per cent predicted lung volumes (PPLV) and percentage of stomach and liver herniation to predict survival. The O/E LHR of less than 25% and O/E TELV of less than 35% have lower survival. Liver herniation of less than 25% and stomach herniation of less than 50% have significantly higher survival and are associated with defect size. The LHR correlated with liver herniation and defect size.<sup>1,3,25</sup> The presence of a hernia sac improves survival, but morbidity remains controversial. There is no cytogenetic anomaly in genetics testing associated with CDH. Right-side CDH is less common and has a worse prognosis than LCDH.<sup>26</sup> No statistically significant difference was associated with survival in birth weight, gestational age (GA) at diagnosis and birth, sex infant and maternal age at left side isolated CDH.<sup>27</sup>

Large-size defects in CDH have a higher risk of significant pulmonary morbidity and long-term pulmonary outcomes than small-size defects. Pulmonary morbidity, including pulmonary hypertension, extracorporeal life support, mechanical ventilation and neonatal intensive care unit days. Long-term pulmonary care, including asthma, rehospitalisation, obstructive lung disease and comprehensive multidisciplinary CDH clinic.<sup>28</sup> Early onset of respiratory distress in neonates with CDH is a poor prognosis and may indicate the presence of more severe pulmonary and cardiac involvement. Pulmonary hypoplasia is an early presentation of respiratory distress. Late respiratory distress has a better prognosis.<sup>29</sup> Late cord clamping results better than immediate clamping at the initial resuscitation manoeuvre. Late cord clamping has a better effect on Apgar score, mean blood pressure and lactate level.<sup>30</sup>

## CONCLUSION

The physiological indexes referred to the 3-stability (fluid balance/electrolyte, temperature and acidbase) and cardiorespiratory stability (OI  $\leq$  9.4, echocardiogram-estimated pulmonary artery pressure  $\leq$  80% systemic blood pressure). In detail, the clinical indicators are urine output  $>$  1 ml/kgBW, Fi O<sub>2</sub>  $<$  0.5, 95% oxygen saturation, normal temperature, lactate  $<$  3 mmol/L, pulmonary arterial blood pressure less than systemic pressure ( $\leq$  80%) and OI  $\leq$  9.4. The first pre-operative 24-hour OI mean was temporally reliable and representative (ICC = 0.70, 95% CI = 0.61–0.77). Within any severity level, there were significant differences in 90-day survival or mortality rate between DR and ER ( $p = 0.002$ ). As a result, there is no optimal timing for surgery in severe cases of CDH. A delay in repair did not predict an increased risk of death, nor did it suggest an increased need for post-operative ECMO. Research shows that regardless of the illness's severity,

the timing of CDH repair does not affect the mortality rate. The limitation of this systematic review was no studies addressed existing stability and prognostic factors. Further research will be carried out using 3-stability, cardiorespiratory stability and prognostic factors.

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## CONFLICT OF INTEREST

None

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## AUTHORS' CONTRIBUTIONS

HP, DA, PGH, MJ and G prepared the conception and design. HP, DA and MJ drafted the article. PGH and G carried out a critical revision of the article, which is essential intellectual content. HP, DA, PGH, MJ and G approved the final paper.

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