Peer Review File
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Reviewer A
Comment 1: The manuscript provides a comprehensive literature review on congenital diaphragmatic hernia, covering both foundational knowledge and recent research. It offers valuable insights into the disease and identifies future research needs. Overall, it merits publication. However, Table 1 needs revision for improved clarity. The criteria for inclusion and exclusion, as well as the selection process, were not made clear.

Reply 1: Thank you so much for this review. We appreciate the feedback. We have improved table 1 by adding more detailed language specifying the inclusion criteria, selection process, and specific exclusion criteria.
The changes made in the text are shown below: See page 18, line 499.
Inclusion criteria included, free full text, clinical trial, meta-analysis, randomized control trails, review, systemic Review, and English language.
There were no specific exclusion criteria
The selection process included identification of articles identified by the first author and confirmed by the senior author and was conducted by these two authors independently.

Reviewer B
Comment 1: The article titled "Recent advances in the treatment of complex congenital diaphragmatic hernia" provides a comprehensive overview of the pathophysiology, etiology, and the latest treatment approaches for this challenging condition. The authors have done an excellent job in presenting a well-written and informative review.
The paper begins by delving into the mechanisms underlying the development of complex congenital diaphragmatic hernia. The authors discuss the intricate interplay of genetic factors, prenatal insults, and abnormal diaphragmatic development, providing a clear understanding of the disease's origins.
Furthermore, the article thoroughly explores the pathophysiological consequences of complex congenital diaphragmatic hernia, emphasizing the respiratory and cardiovascular challenges faced by affected infants. The authors adeptly explain the impact of diaphragmatic defects on lung development, pulmonary hypertension, and cardiac dysfunction.
One of the standout features of this review is its focus on recent advancements in the treatment of complex congenital diaphragmatic hernia. The authors meticulously discuss the evolving fetal intervention, highlighting the improvements in outcomes and long-term prognosis.
The article is well-structured, with a logical flow of information that allows the reader to grasp the complex nature of the condition easily. The authors provide a balanced perspective by discussing the challenges associated with current treatment strategies, while also highlighting the promising research directions and future possibilities.

In conclusion, "Recent advances in the treatment of complex congenital diaphragmatic hernia" is an outstanding review article that encompasses the breadth of knowledge regarding this condition. The authors' meticulous approach in presenting the pathogenesis, pathophysiology, and latest treatment modalities makes this paper a valuable resource for clinicians, researchers, and healthcare professionals involved in the care of infants with complex congenital diaphragmatic hernia. I extend my sincere appreciation to the authors for their excellent contribution.

Reply 2: We deeply appreciate the kind words from reviewer B. There have been no changes made to the manuscript based on this review.

Reviewer C
Comment 1: In the abstract, the first sentence of “Key Content and Findings” seems to be a restatement from the introduction. Would suggest putting in only one of the spots.

Reply 1: Thank you for the feedback. We have adjusted the first sentence for the “key content and findings”.
The changes that have been made are seen below: See page 2, line 73-74.
Congenital diaphragmatic hernia (CDH) is a congenital anomaly of the cardiopulmonary and diaphragmatic systems that represents a spectrum of disease.

Comment 2: Page 5, lines 128-130, I would suggest also adding percent predicted lung volume (PPLV) as that is used in some institutions and a recognized prenatal predictor. It is also referred to later in the manuscript so would introduce that here.

Reply 2: Thank you for this recommendation. We agree that adding percent predicted lung volume added to the overall manuscript and introducing it here was necessary. We have introduced the concept here and elaborate on it further down in the article.
The changes are shown below: See page 4, line 124.
High-risk CDH can be defined in a number of ways: through the CDHSG diaphragm defect grading system (typically C and D defects, Figure 1),(8) multiple published risk stratification equations,(9) lung-to-head ratio (LHR, typically <1.0), precent predictive lung volumes (PPLV), observed-to-expected (O/E) LHR (typically <25%), O/E total fetal lung volumes (TFLV, typically <25%), and/or liver herniation (typically >20% on magnetic resonance imaging (MRI)).(10, 11, 12)

Comment 3: I liked table 2 which described the cardiopulmonary phenotypes however I think it would be of benefit to the reader to add a row at the bottom that describes optimal treatment of each phenotype (as described on pages 9-10 lines 250-254).

Reply 3: Thank you for this recommendation. The addition of this better completes the table and the visual understanding of each phenotype. We have added the various treatment options for each phenotype as seen below and on page 19, line 507

Comment 4: Page 11, line 297 describes “prostacyclin (PGI2)” which seems to be misplaced. The authors were previously discussing PGE1 treatment and not sure how it transitioned to PGI2. Would introduce the new therapy better or move to another location.

Reply 4: We appreciate this comment and agree that discussion of PG12 was out of context. We have removed the topic of PG12 and reworded in a later section of the paper.
Please see below the following addition that was made later in the paper. See page 16, line 460-462.
For example, early prostacyclin (PG12) therapy may decrease the need and/or duration of ECLS and the administration of amniotic fluid stem cell extracellular vesicles (AFSC-EVs) may be a way to rescue pulmonary hypoplasia.(46)

Interventions and Therapies	Changes in ventilator settings	Reducing pre-capillary PVR by optimizing sedation, vasodilation, and lung recruitment	Supporting LV function with inotropic therapies

Comment 5: Page 12, lines 332-335, this list should also include PPLV (as suggested in #2 above).

Reply 5: Thank you again for recommending we elaborate and include PPLV in the discussion of this paper. PPLV was mentioned early in the paper as recommended by an early comment by Reviewer C, but in response to this comment, we have included PPLV in the list of predictive measurements.
See page 11 and line 326-328.
Prenatally, image derived measurements best predict high risk CDH. The most frequently obtained and investigated imaging findings include lung-to-head ratio (LHR), observed-to-expected (O/E) LHR, O/E total fetal lung volumes (TFLV), absolute fetal lung volume (FLV), percent predicted lung volumes (PPLV), percentage of liver herniation, and stomach herniation.

Comment 6: Page 13, line 363, uses PPLV and this hasn’t been introduced.

Reply 6: Thank you for this recommendation. We have included PPLV earlier in the manuscript per earlier recommendations.

Comment 7: Page 14, lines 386-387, need to include values for PPLV

Reply 7: Thank you for this recommendation. We have included the values for PPLV as seen below.
Please see page 12, line 338-341.

PPLV is a newer measure that is based off lung volumes and fetal size that was found to be a much more intuitive measurement with studies showing that values less than 15 were associated lower survival rates, longer lengths of stay, and prolonged ECLS courses. (33)

Comment 8: Page 17, lines 451-452, would restate as “a significantly higher survival to discharge (40%) compared to those who received expectant care (15%)” for the reader who is less familiar with the findings of the study.

Reply 8: Thank you for the recommendation and the clarification in verbiage. We have made the following recommend changes as seen below.
Please see page 16, line 452-453.
A randomized trial completed by J Deprest et al shows that by performing FETO in fetuses between 27-29 weeks gestation there is a significantly higher survival to discharge (40%) compared to those who received expectant care (15%).(45)

Reviewer D
Comment 1: There have been numerous reviews on this subject and indeed guidelines, the authors need to better emphasize the need for their review.

Reply 1: We appreciate this comment and while there are many reviews on CDH overall, but we believe a review that focuses on highest risk or more complex CDH is both timely and necessary given the rapid advances in the treatment options and advances. The final sentence of the first paragraph of the introduction was edited to reiterate this. See the changes below. Page 4, line 119-120
This fact underscores the importance of this review’s focus on addressing the needs of this patient population.

Comment 2: The abstract needs to be more informative regarding the key findings

Reply 2: We appreciate this comment and those seen in the the editorial comments and have focused the abstract and made a made a more concise abstract focusing on the key findings. Please see the fully revised and tailored introduction. See page 2, line 72-79.

Comment 3: The authors need to include discussion on different surgical management and postnatal interventions.

Reply 3: Thank you for this comment. We have added the following statement to clarify the discussion on surgical management.
See Page 13, lines 372-375.
After stabilization, patients who do not receive ECLS typically undergo CDH repair surgery after 24 hours of life but within the first seven days of life. The optimal timing and surgical technique used for repair with vary depending on the severity of CDH and the presence of any additional anomalies, which exceeds the scope of this review.

Comment 4: Similarly with regard to postnatal prediction of outcome.

Reply 14: We appreciate this comment and we have discussed this between pages 12 lines 343-353.

Comment 15: The figures not additive.

Reply 15: We appreciate your perspective but hope by adding figure ledges and optimizing the tables as commented by the other reviewers we have created are more informative figures. Please see the updated figures on pages 20-22.

Comment 16: There are typos and the English need to be improved.

Reply 16: We appreciate this and have reviewed the entire manuscript hopefully catching any errors and typos.