frontiers | Research Topics

Respiratory support: Clinical applications and the novel future

Edited by
Jun Duan, Bing Dai and Antonio M. Esquinas

Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-4610-9
DOI 10.3389/978-2-8325-4610-9

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Respiratory support: Clinical applications and the novel future

Topic editors

Jun Duan – First Affiliated Hospital of Chongqing Medical University, China

Bing Dai – The First Affiliated Hospital of China Medical University, China

Antonio M. Esquinas – Hospital General Universitario Morales Meseguer, Spain

Citation

Duan, J., Dai, B., Esquinas, A. M., eds. (2024). *Respiratory support: Clinical applications and the novel future*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-4610-9

Table of contents

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 05 December 2022
DOI 10.3389/fmed.2022.1050784

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Cristian Deana,
Azienda Sanitaria Universitaria Integrata di Udine, Italy
Richard M. Pino,
Louisiana State University, United States

*CORRESPONDENCE
Kentaro Yamakawa
KYamakawa@jikei.ac.jp

SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 22 September 2022
ACCEPTED 17 November 2022
PUBLISHED 05 December 2022

CITATION
Kuwabara Y, Yamakawa K, Okui S, Miyazaki E and Uezono S (2022) Association between surgical tracheostomy and chronic tracheal stenosis: A retrospective, single-center study.
Front. Med. 9:1050784.
doi: 10.3389/fmed.2022.1050784

Association between surgical tracheostomy and chronic tracheal stenosis: A retrospective, single-center study

Yuki Kuwabara, Kentaro Yamakawa*, Seiko Okui, Erica Miyazaki and Shoichi Uezono

Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

Background: Tracheal stenosis is a major complication of tracheostomy. Accordingly, anesthesiologists tend to select a smaller endotracheal tube (ETT) than usual for patients with a prior tracheostomy history, regardless of the presence or absence of respiratory symptoms. However, it likely comes from our trial and error, not scientific evidence. Therefore, in this study, we retrospectively examined the association between traditional surgical tracheostomy and tracheal stenosis as assessed by transverse computed tomography (CT).

Methods: Patients who underwent surgery for head and neck cancer from January 2010 to December 2013, with a temporary tracheostomy closed within a couple of months, were included. Exclusion criteria were tracheostoma before surgery, permanent tracheostomy, or insufficient CT follow-up. Transverse CT slices were measured 2 cm above and below the tracheostomy site (0.5 cm/slice for a total of 9 slices). The minimum cross-sectional tracheal area and horizontal and vertical diameters in transverse CT slices were compared before (baseline: BL), 6 months (6M) and 12 months (12M) after tracheostomy. Tracheal stenosis was defined as a decrease in the minimum cross-sectional tracheal area compared to BL.

Results: Of 112 patients, 77 were included. The minimum tracheal area was significantly decreased at 6M and 12M compared to BL (BL: mean 285 [SD 68] mm^2, 6M: 267 [70] mm^2, $P < 0.01$ vs. BL, 12M: 269 [68] mm^2, $P < 0.01$ vs. BL), and the localization was predominantly at or above the tracheostomy site at 6M and 12M. Tracheal stenosis was identified in 55 patients at 6M and in 49 patients at 12M without any respiratory symptoms. With regard to horizontal and vertical diameter, only horizontal diameter was significantly decreased at 6M and 12M compared to BL (BL: 16.8 [2.4] mm, 6M: 15.4 [2.7] mm, $P < 0.01$ vs. BL, 12M: 15.6 [2.8] mm, $P < 0.01$ vs. BL).

Conclusion: Conventional surgical tracheostomy was associated with a decreased horizontal diameter of the trachea. It resulted in a decreased cross-

sectional tracheal area in more than one-half of the patients; however, no patient complained of any respiratory symptoms. Therefore, even without respiratory symptoms, prior tracheostomy causes an increased risk of tracheal stenosis, and using a smaller ETT than usual could be reasonable.

KEYWORDS

tracheal stenosis, surgical tracheostomy, triangulation, intubation, computed tomography

Introduction

Tracheostomy is commonly performed in cases of upper airway obstruction and for patients who require prolonged mechanical ventilation (1). The benefits of tracheostomy include upper airway management, as well as decreased risk of ventilator-associated pneumonia in patients intubated long-term (2, 3). However, a tracheostomy can alter the tracheal shape around the surgical site to result in an A-frame or triangular-shaped deformity (4–6), which can lead to tracheal stenosis (7). Tracheal stenosis of > 30% to 50% of the original size is thought to cause respiratory symptoms, and the incidence of symptomatic tracheal stenosis after tracheostomy is reported to be 1 to 6% (7–9). On the other hand, asymptomatic tracheal stenosis after tracheostomy has not been well examined (10, 11), since mild tracheal stenosis is not often subject to active treatment. Regardless of the respiratory symptom, anesthesiologists tend to select a smaller endotracheal tube (ETT) than usual in general anesthesia for patients with a prior tracheostomy history without distinct scientific evidence.

At our institute, otolaryngologists perform a surgical tracheostomy to prevent postoperative upper airway obstruction during surgery for head and neck tumorectomy and flap reconstruction. The tracheostomy is usually closed for about a month once respiratory safety is confirmed. And their cancer follow-up is performed with imaging over time, including trachea around tracheostomy. Some of these patients without any respiratory symptoms may visit an operation room again to undergo a different kind of surgery. In such cases, the choice of ETT is sometimes discussed.

Therefore, the purpose of the present study was to retrospectively examine the association of conventional surgical tracheostomy with asymptomatic tracheal stenosis over time as measured by transverse computed tomography (CT) in head and neck cancer patients.

Materials and methods

This retrospective study was approved by the Jikei University Certified Review Board, which provided a waiver of written informed consent (number 29-127[8743]). This study was conducted in accordance with the principles of the Helsinki Declarations.

Patients who underwent head and neck cancer surgery from January 2010 to December 2013, with a temporary tracheostomy closed within a couple of months, were included in the study. Exclusion criteria were tracheostoma before surgery, permanent tracheostomy, or insufficient CT follow-up. Patients were performed a tracheostomy with a U-shaped tracheal incision under general anesthesia, and ventilated through the tube in the tracheostoma during the surgery. After respiratory safety was confirmed, the tracheostomy tube was removed to close the site.

Data collection and tracheal measurement

Demographic information, including age, sex, height, body weight, body mass index, and medical history, was reviewed and collected from medical records. All patients underwent CT before (baseline [BL]) and after surgery at 6 months (6M) and 12 months (12M) for cancer evaluation. The presence and extent of tracheal stenosis were analyzed retrospectively using the CT images, which were set to 0.5 cm per slice. In the transverse plane, cross-sectional tracheal area and vertical and horizontal diameters were measured for each of the 9 slices over a distance of 4 cm (2 cm above and below the tracheostomy site). The cross-sectional tracheal area was calculated by tracing around the trachea, and diameters were measured by determining 2 sites of the tracheal wall in each of the horizontal and vertical directions (**Figure 1**) with picture archiving and communication system image display (Synapse; Fujifilm Corp., Tokyo, Japan). The minimum cross-sectional area for each patient at each time point (BL, 6M, and 12M) was used for analysis. Tracheal stenosis was defined as a decrease of the minimum cross-sectional area at 6M or 12M compared to BL.

Statistical analysis

Statistical analysis and figure creation were performed with GraphPad Prism software (version 8, GraphPad Software Inc., San Diego, CA) and JMP Pro 16.0.0 (512340) (SAS

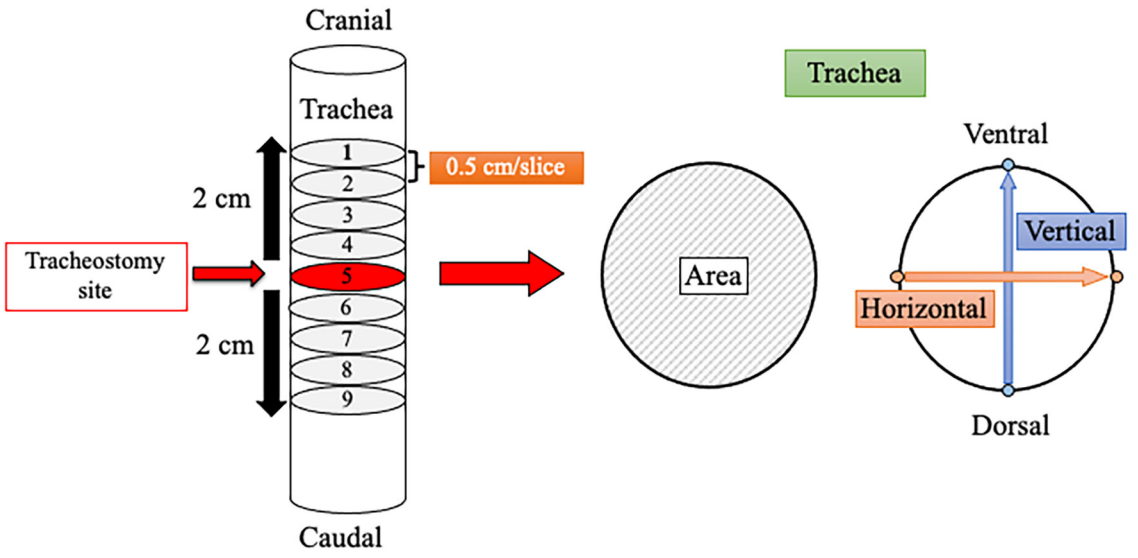


FIGURE 1
Schematic of a method for measuring the tracheal lumen using computed tomography. Measurement was performed over a distance of 4 cm above and below the tracheostomy site. Each image slice was set to 0.5 cm, and 9 slices were analyzed. The minimum tracheal area among the 9 slices was selected for each time point (baseline, 6 months, and 12 months). Horizontal and vertical tracheal diameters were also measured.

Institute., Cary, NC, USA). Statistical normality was confirmed with the Shapiro-Wilk test. Quantitative data are presented either as mean [SD] or median [first, third quartile], per statistical normality, and qualitative data are presented as *n* (%). A one-way repeated-measures analysis of variance with a Tukey *post hoc* test or Friedman test with a Dunn *post hoc* test was performed to test tracheal measurements per statistical normality. A *P* value <0.05 was considered statistically significant.

Result

A total of 112 patients who underwent surgery and tracheostomy were identified, and 77 were deemed eligible for analysis (Figure 2). Patient demographic characteristics are summarized in Table 1. The average age was 62 (11) years, and 57 (74%) patients were male. A total of 55 (71%) patients were smokers. The average time to tracheostomy closure was 34 (14) days.

No patients had any respiratory symptoms.

The minimum cross-sectional tracheal area was significantly decreased at 6M and 12M after tracheostomy compared to BL (BL: 285 [68] mm^2; 6M: 267 [70] mm^2, $P < 0.01$ vs. BL; 12M: 269 [68] mm^2, $P < 0.01$ vs. BL) (Figure 3A). Of the 77 analyzed patients, tracheal stenosis was observed in 55 (71.4%) patients by 11.9% (9.4%) at 6M, and in 49 (63.6%) patients by 12.2% (8.8%) at 12M.

With respect to horizontal and vertical tracheal diameters, the horizontal diameter was significantly decreased compared to BL (BL: 16.8 [2.4] mm, 6M: 15.4 [2.7] mm, $P < 0.01$ vs. BL, 12M: 15.6 [2.8] mm, $P < 0.01$ vs. BL) (Figure 3B). The change in the horizontal diameter compared to BL was –8.1% [12%] at 6M and –7.1% [12%] at 12M. Figure 4 demonstrates the horizontal diameter distribution in each patient's minimum cross-sectional area at BL, 6M (Figure 4A) and 12M (Figure 4B).

No significant difference was observed for vertical diameter (BL: 19.5 [17.2, 22.8] mm, 6M: 20.7 [17.6, 22.3] mm, $P = 0.23$ vs. BL, 12M: 19.7 [17.5, 22.5] mm, $P = 0.32$ vs. BL) (Figure 3C).

The minimum cross-sectional area for the 9 CT slices for each patient was localized to the most caudal or cranial level at BL (Figure 5A). It was predominantly at or above the tracheostomy site at 6M and 12M (Figures 5B,C). Conversely, the localization of the maximal tracheal area was predominantly below the tracheostomy site (caudally) at 6M and 12M (Figures 6B,C), whereas no predominant localization was observed at BL (Figure 6A).

TABLE 1 Patient demographic characteristics (*n* = 77).

Age, y, mean (SD)	62 (11)
Sex (male/female), *n* (%)	57 (74)/20 (26)
Height, cm, mean (SD)	163.4 (7.9)
Body weight, kg, mean (SD)	58.8 (11.3)
Body mass index, kg/m^2, mean (SD)	21.9 (3.3)
Hypertension, *n* (%)	34 (44.2)
Diabetes, *n* (%)	12 (15.6)
COPD, *n* (%)	8 (10.4)
Smoker, *n* (%)	55 (71.4)

COPD, chronic obstructive pulmonary disease.

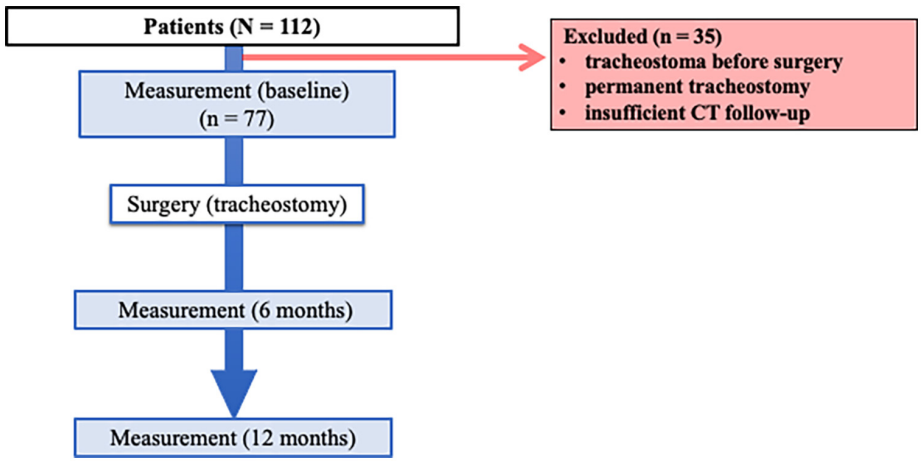


FIGURE 2
Flow of study protocol. Of 112 patients who underwent surgery for neck and head cancer, 77 were included in the study. Computed tomography was performed before surgery (baseline) and at 6 and 12 months after surgery.

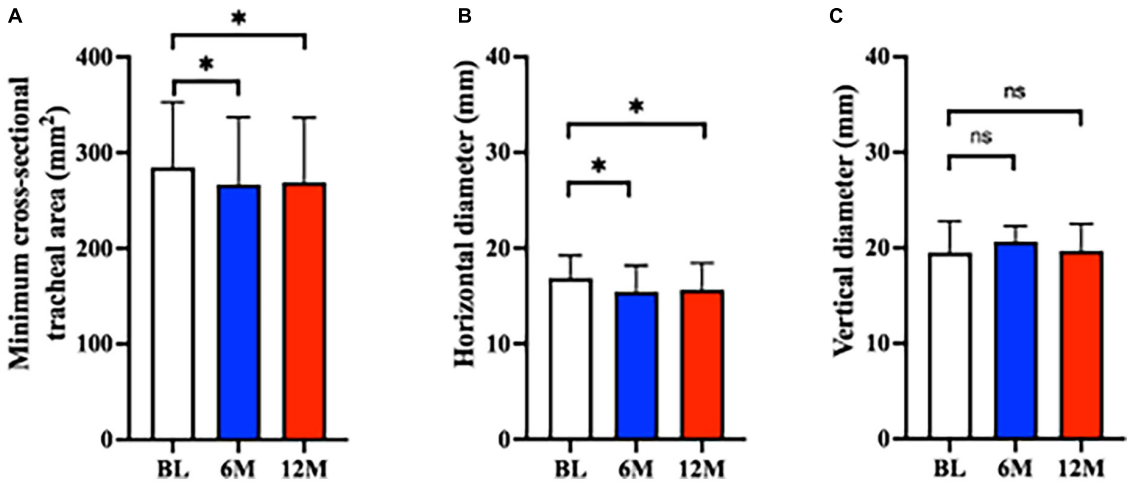


FIGURE 3
Tracheal stenosis after tracheostomy. The minimum tracheal area decreased significantly at 6M and 12M (both $P < 0.01$ vs. BL). There was no difference between 6M and 12M ($P = 0.66$). *$P < 0.01$. **(B)** The horizontal tracheal diameter decreased significantly at 6M and 12M compared to BL (both $P < 0.01$ vs. BL). There was no difference between 6M and 12M ($P = 0.43$). *$P < 0.01$. **(C)** The vertical diameter did not change over time (6M: $P = 0.23$ vs. BL; 12M: $P = 0.32$ vs. BL). No change was observed between 6M and 12M ($P > 0.99$). Bar graphs are shown as mean ± SD **(A,B)** and median, first, and third quartile **(C)**. 6M: 6 months after surgery, 12M: 12 months after surgery, BL: baseline, ns, not significant.

Discussion

We measured tracheal area and diameter in CT to assess tracheal stenosis by tracheostomy and demonstrated decreased tracheal area and horizontal diameter. Our results showed that conventional surgical tracheostomy was associated with (1) a decrease of the minimum cross-sectional tracheal area in more than one-half of patients at 6M (11.9% area reduction), which was maintained at 12M (12.2% area reduction) without any respiratory symptom, (2) localization of the minimum cross-sectional area in the cranial direction and the maximum tracheal area in the caudal direction from the tracheostomy site, and (3) a significantly decreased horizontal tracheal diameter at 6M and 12M compared to BL without changes in vertical diameter. In addition, the alteration causes a trachea for triangular-shaped stenosis after tracheostomy (Figure 7).

In most reports regarding tracheostomy, bronchoscopy has been used to assess for tracheal stenosis (12). However, detailed changes in tracheal diameter by numerical value cannot be measured by bronchoscopy, and it is relatively invasive compared to CT (13–16). Thus, this is the first

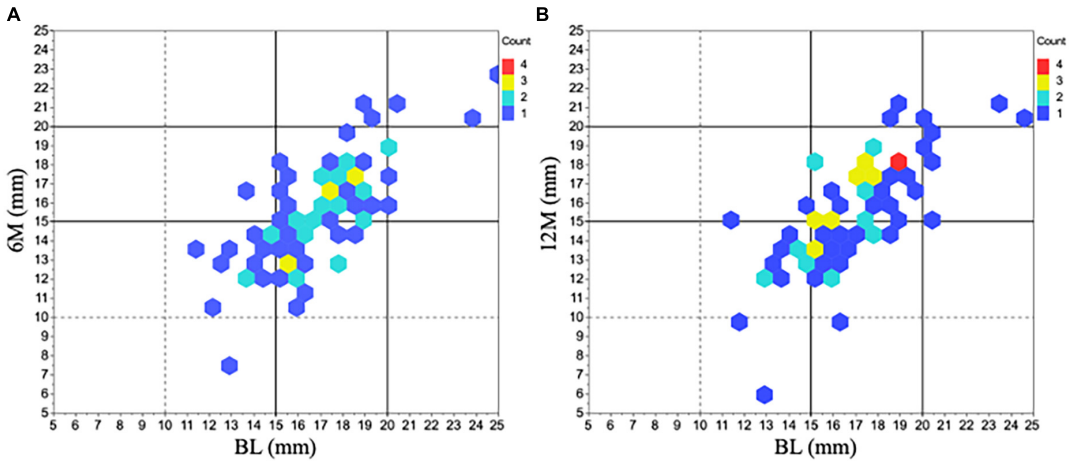


FIGURE 4
Horizontal diameter changes in minimum tracheal area before and after tracheostomy. The distribution of horizontal diameter changes in all 77 patients was represented at 6M **(A)** and 12M **(B)** compared to BL. The most predominant range in the initial horizontal diameter was within 15 ~ 20 mm at BL (n = 56). After tracheostomy, many of the diameters shifted shorter than the initial one. 6M: 6 months after surgery, 12M: 12 months after surgery, BL: baseline.

study to show detailed tracheal measurements over time in patients with asymptomatic tracheal stenosis after conventional surgical tracheostomy.

Tracheal stenosis – decreased area after tracheostomy

The incidence and degree of chronic tracheal stenosis after surgical tracheostomy of the intact trachea, which closes for about a month, especially how the tracheal lumen changes during follow-up, has not been fully elucidated. James et al. studied tracheal stenosis after surgical tracheostomy in maxillofacial surgery and reported 8.8% without any respiratory symptoms (11). In that study, they measured the shortest anteroposterior or transverse tracheal diameter with CT or magnetic resonance imaging. They demonstrated the tracheal stenosis as the change in diameter, not a numerical value. We speculate that the different incidences between the two studies were the different definitions of tracheal stenosis and the various duration of the cannulation period. We defined tracheal stenosis as a decrease in the minimum cross-sectional tracheal area compared to BL, because our focus was on overall tracheal deformity, including the examination of horizontal and vertical diameters. Furthermore, the longer intubation period in the present study (34 [13] days) might have increased the number of patients with tracheal stenosis (7, 11, 17).

TABLE 2 Endotracheal tube diameter measurements.

Manufacturer	Inner diameter (mm)	Outer diameter (mm)
Covidien, Hi-Lo	8.0	10.8
	7.5	10.2
	7.0	9.5
	6.5	8.9
	6.0	8.2
Teleflex, Hi-Lo	8.0	11.4
	7.5	10.9
	7.0	10.4
	6.5	9.9
	6.0	9.4
Smiths Medical, Hi-Lo	8.0	10.9
	7.5	10.3
	7.0	9.6
	6.5	8.9
	6.0	8.2

Also, concerning the comparison to percutaneous dilatational tracheostomy (PDT), PDT has been widely accepted as an alternative surgical tracheostomy and is considered a safe strategy (18–20). An observational study demonstrated that 15 (31%) of 48 long-term PDT patients (average 30 months observation) developed tracheal stenosis more than 10% in diameter by CT measurement. Furthermore, one (2%) patient had severe stenosis, a greater than 50% reduction from the original trachea (21). The present study showed that 27 (35%) patients decreased tracheal area by more than 10% from the original trachea at 12M, and one patient decreased by more than 50% at 6M, followed by 30% at 12M. The definitions of tracheal stenosis were different (tracheal diameter narrowing vs.

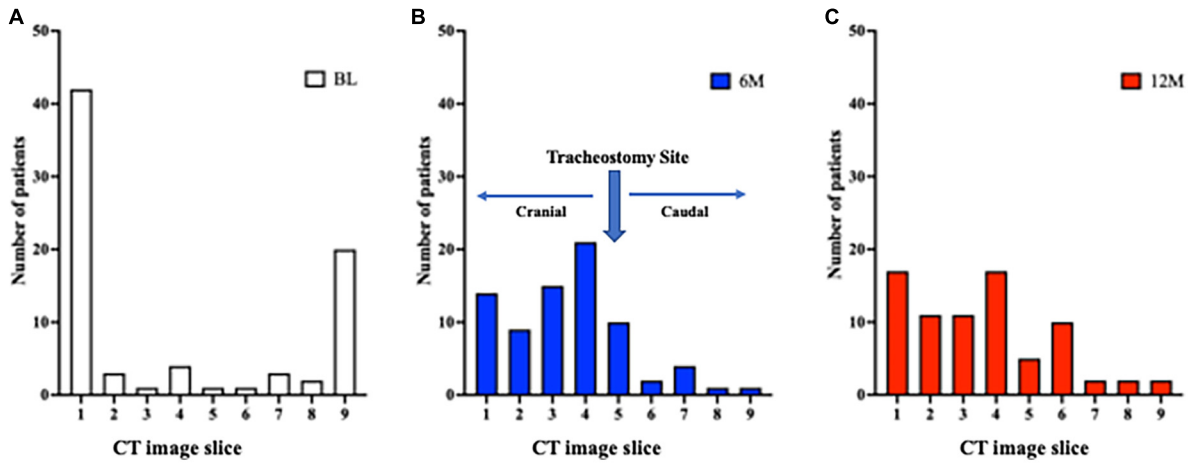


FIGURE 5
Localization of the site of minimum tracheal area before and after tracheostomy. **(A)** A total of 9 CT slices were obtained for each patient (cranial to caudal, with tracheostomy site in the middle [slice 5]). At BL, the site of minimum tracheal area was at the most cranial (slice 1) or most caudal (slice 9) slice. **(B,C)** At 6M and 12M, the site of minimum tracheal area was predominantly at or above the tracheostomy site. 6M: 6 months after surgery, 12M: 12 months after surgery, BL: baseline, CT: computed tomography.

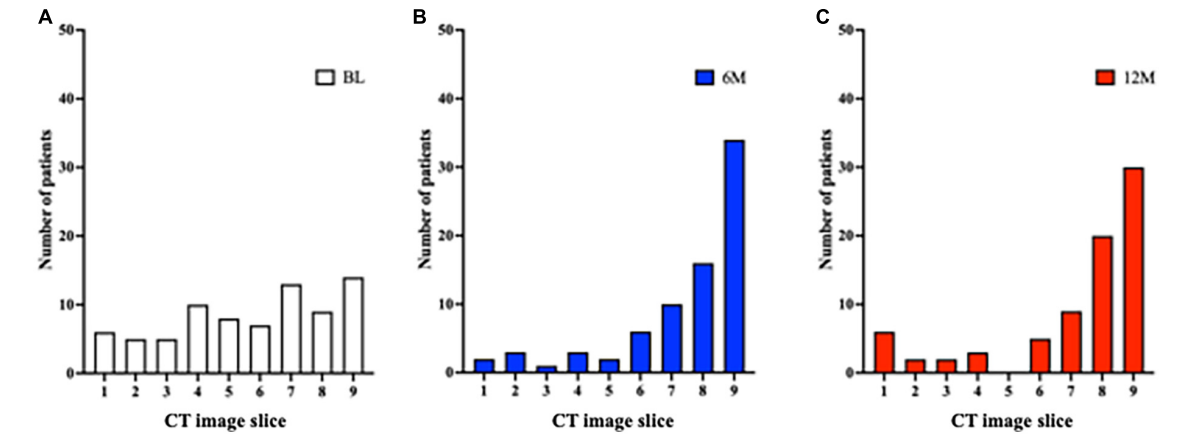


FIGURE 6
Localization of the site of maximum tracheal area before and after tracheostomy. **(A)** A total of 9 CT slices were obtained for each patient (cranial to caudal, with tracheostomy site in the middle [slice 5]). At BL, there was no predominant localization of the site of maximum tracheal area. **(B,C)** At 6M and 12M, the site of maximum tracheal area was localized below the tracheostomy site (caudally). 6M: 6 months after surgery, 12M: 12 months after surgery, BL: baseline, CT: computed tomography.

tracheal area reduction), but surgical tracheostomy can be comparable with PDT from the point of tracheal stenosis after tracheostomy.

In the localization of tracheal stenosis, the minimum tracheal area was seen at the proximal and distal locations at BL, where there might be difficulty with intubation, even in patients without stenosis. After tracheostomy, the minimum tracheal area was predominantly observed above the tracheostomy site, consistent with prior reports examining symptomatic tracheal stenosis or deformity by endoscopy (6, 12). On the other hand, the maximum area was broadly distributed across the trachea at BL. Interestingly, we found that the maximum tracheal area was localized in the caudal direction when the tracheostomy tube was placed for approximately a month until respiratory safety was confirmed; this might prevent the development of granulation tissue and resulting stenosis.

Tracheal stenosis – decreased horizontal diameter after tracheostomy

In the present study, the horizontal diameter decreased by 1.2 to 1.4 mm from BL over time, but the vertical diameter

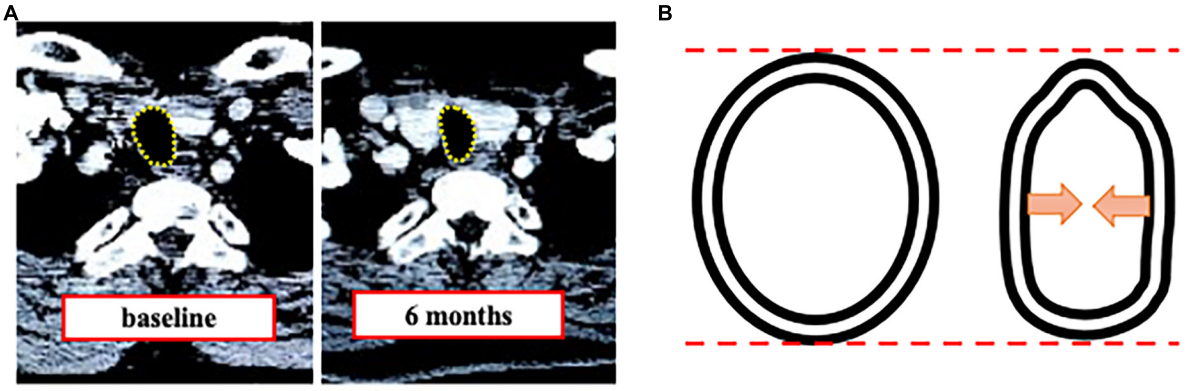


FIGURE 7
Tracheal stenosis after tracheostomy. **(A)** Representative computed tomography image of tracheal stenosis. **(B)** Schematic showing triangulation after tracheostomy.

did not change compared to BL. This heterogeneous change caused tracheal deformity, leading to tracheal stenosis (Figure 7) (4, 22). Although it has been reported that tracheostomy can cause tracheal stenosis due to the alteration of the trachea to be a triangular shape (14), there have been no prior studies on how much each diameter changes after conventional surgical tracheostomy for the horizontal and vertical direction. The evidence of the decreased horizontal diameter gives anesthesiologists useful information to select an ETT.

Tracheal stenosis and endotracheal tube selection

Patients with a triangular-shaped trachea can be difficult to intubate (5). As shown in Figure 4, the horizontal diameter of many patients in the present study was 15.0 ∼ 19.9 mm at BL. Then after tracheostomy, the horizontal diameter decreased to 10.0 ∼ 14.9 mm in almost half of the study population. Of note, the decrease of the horizontal diameter after tracheostomy was 1.4 [1.9] mm at 6M and 1.2 [1.9] mm at 12M, which was very variable. Comparing various types of available ETTs (Table 2), all with an inner diameter of ≥7.5 mm have an outer diameter of > 10.0 mm. In addition, it is important to consider the cuff when selecting the ETT because it could get stuck if the outer diameter is close to the shortest horizontal diameter in the trachea. These facts show us that downsizing ETT might be reasonable for a patient with a short horizontal diameter of less than 14.9 mm before tracheostomy to prevent airway trouble, regardless of respiratory symptoms.

We suggest that anesthesiologists evaluate neck CT images if available to ensure an appropriate ETT size with the right cuff volume is selected before intubation for patients with a history of surgical tracheostomy because of variable changes in tracheal diameter. We believe that the present study provides anesthesiologists with practical information regarding the right selection of ETTs with asymptomatic tracheal stenosis after tracheostomy and the usefulness of neck CT for preoperative evaluation.

Limitations

This study has a few limitations. First, this was a retrospective study, and causality was not assessed. Second, several reports indicate that cuff pressure is a risk factor for tracheal stenosis (9, 23); however, all of the patients in this study underwent tracheostomy during surgery, and cuff pressure was monitored right after intubation. Third, we analyzed a total distance of 4 cm (2 cm above and below the tracheostomy site) by transverse-plane CT, not the entire trachea (24). However, we focused on the relationship between tracheostomy and tracheal stenosis. We believe that assessment 2 cm above and below the tracheostomy site is enough to evaluate for tracheal stenosis before surgery.

Conclusion

The present CT study detailed the development of asymptomatic tracheal stenosis after tracheostomy. Even in patients without respiratory symptoms, the decreased cross-sectional tracheal area at 6M and 12M after tracheostomy appeared to be due to a decrease in horizontal tracheal diameter. The use of CT can help to evaluate tracheal stenosis before anesthesia in patients with prior tracheostomy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Jikei University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YK and KY contributed to the study's conception and design and wrote the manuscript. SO, EM, YK, and KY performed the data collection and analysis. SU supervised this study. All authors have reviewed and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Astrachan DI, Kirchner JC, Goodwin WJ Jr. Prolonged intubation vs. tracheotomy: complications, practical and psychological considerations. *Laryngoscope.* (1988) 98:1165–9. doi: 10.1288/00005537-198811000-00003

2. Nseir S, Di Pompeo C, Jozefowicz E, Cavestri B, Brisson H, Nyunga M, et al. Relationship between tracheotomy and ventilator-associated pneumonia: a case control study. *Eur Respir J.* (2007) 30:314–20. doi: 10.1183/09031936.06.00024906

3. Freeman BD, Morris PE. Tracheostomy practice in adults with acute respiratory failure. *Crit Care Med.* (2012) 40:2890–6. doi: 10.1097/CCM.0b013e31825bc948

4. Plojoux J, Laroumagne S, Vandemoortele T, Astoul PJ, Thomas PA, Dutau H. Management of benign dynamic "A-shape" tracheal stenosis: a retrospective study of 60 patients. *Ann Thorac Surg.* (2015) 99:447–53. doi: 10.1016/j.athoracsur.2014.08.037

5. Fernando RJ, Madden LL. Tracheal a-frame deformity: a challenging variant of tracheal stenosis. *Anesthesiology.* (2018) 128:1240. doi: 10.1097/ALN.0000000000002109

6. Kennedy AA, De Alarcon A, Tabangin ME, Rutter MJ, Myer CMT, Smith MM, et al. Tracheal a-frame deformities following airway reconstruction. *Laryngoscope.* (2021) 131:E1363–8. doi: 10.1002/lary.28996

7. Johnson RF, Saadeh C. Nationwide estimations of tracheal stenosis due to tracheostomies. *Laryngoscope.* (2019) 129:1623–6. doi: 10.1002/lary.27650

8. Dempsey GA, Morton B, Hammell C, Williams LT, Tudur Smith C, Jones T. Long-term outcome following tracheostomy in critical care: a systematic review. *Crit Care Med.* (2016) 44:617–28. doi: 10.1097/CCM.0000000000001382

9. Li M, Yiu Y, Merrill T, Yildiz V, Desilva B, Matrka L. Risk factors for posttracheostomy tracheal stenosis. *Otolaryngol Head Neck Surg.* (2018) 159:698–704. doi: 10.1177/0194599818794456

10. Heffner JE, Miller KS, Sahn SA. Tracheostomy in the intensive care unit. Part 2: complications. *Chest.* (1986) 90:430–6. doi: 10.1378/chest.90.3.430

11. James P, Parmar S, Hussain K, Praveen P. Tracheal stenosis after tracheostomy. *Br J Oral Maxillofac Surg.* (2021) 59:82–5. doi: 10.1016/j.bjoms.2020.08.036

12. Bergeron M, Qualls H, De Alarcon A, Rutter MJ. Management of a-frame tracheal deformity in children with endoscopic resection tracheoplasty. *Laryngoscope.* (2021) 131:E719–23. doi: 10.1002/lary.28953

13. Carretta A, Melloni G, Ciriaco P, Libretti L, Casiraghi M, Bandiera A, et al. Preoperative assessment in patients with postintubation tracheal stenosis : rigid and flexible bronchoscopy versus spiral CT scan with multiplanar reconstructions. *Surg Endosc.* (2006) 20:905–8. doi: 10.1007/s00464-005-0475-0

14. Shin B, Kim K, Jeong BH, Eom JS, Song WJ, Kim H. Clinical implications of differentiating between types of post-tracheostomy tracheal stenosis. *J Thorac Dis.* (2017) 9:4413–23. doi: 10.21037/jtd.2017.10.99

15. Shepard JO, Flores EJ, Abbott GF. Imaging of the trachea. *Ann Cardiothorac Surg.* (2018) 7:197–209. doi: 10.21037/acs.2018.03.09

16. Aljathlany Y, Aljasser A, Alhelali A, Bukhari M, Almohizea M, Khan A, et al. Proposing an endotracheal tube selection tool based on multivariate analysis of airway imaging. *Ear Nose Throat J.* (2021) 100:629S–35. doi: 10.1177/0145561319900390

17. Goldenberg D, Ari EG, Golz A, Danino J, Netzer A, Joachims HZ. Tracheotomy complications: a retrospective study of 1130 cases. *Otolaryngol Head Neck Surg.* (2000) 123:495–500. doi: 10.1067/mhn.2000.105714

18. Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. *Crit Care.* (2006) 10:R55. doi: 10.1186/cc4887

19. Higgins KM, Punthakee X. Meta-analysis comparison of open versus percutaneous tracheostomy. *Laryngoscope.* (2007) 117:447–54. doi: 10.1097/01.mlg.0000251585.31778.c9

20. Klotz R, Probst P, Deininger M, Klaiber U, Grummich K, Diener MK, et al. Percutaneous versus surgical strategy for tracheostomy: a systematic review and meta-analysis of perioperative and postoperative complications. *Langenbecks Arch Surg.* (2018) 403:137–49. doi: 10.1007/s00423-017-1648-8

21. Norwood S, Vallina VL, Short K, Saigusa M, Fernandez LG, Mclarty JW. Incidence of tracheal stenosis and other late complications after percutaneous tracheostomy. *Ann Surg.* (2000) 232:233–41. doi: 10.1097/00000658-200008000-00014

22. Aloud A. Tracheal stenosis. *Southwest Respir Crit Care Chron.* (2019) 7:57–8. doi: 10.12746/swrccc.v7i28.548

23. Pearson FG, Goldberg M, Da Silva AJ. Tracheal stenosis complicating tracheostomy with cuffed tubes. Clinical experience and observations from a prospective study. *Arch Surg.* (1968) 97:380–94. doi: 10.1001/archsurg.1968.01340030040002

24. LoCicero J, Costello P, Campos CT, Francalancia N, Dushay KM, Silvestri RC, et al. Spiral CT with multiplanar and three-dimensional reconstructions accurately predicts tracheobronchial pathology. *Ann Thorac Surg.* (1996) 62:811–7. doi: 10.1016/S0003-4975(96)00532-7

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 19 January 2023
DOI 10.3389/fmed.2023.1109681

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Jacek Smereka,
Wrocław Medical University, Poland
Venkatakrishna Rajajee,
University of Michigan, United States

*CORRESPONDENCE
Cheuk-Kwan Sun
✉ researchgate000@gmail.com
I-Wen Chen
✉ mavising@gmail.com

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Intensive Care Medicine and Anesthesiology, a section of the journal Frontiers in Medicine

RECEIVED 28 November 2022
ACCEPTED 05 January 2023
PUBLISHED 19 January 2023

CITATION
Tsai W-W, Hung K-C, Huang Y-T, Yu C-H, Lin C-H, Chen I-W and Sun C-K (2023) Diagnostic efficacy of sonographic measurement of laryngeal air column width difference for predicting the risk of post-extubation stridor: A meta-analysis of observational studies.
Front. Med. 10:1109681.
doi: 10.3389/fmed.2023.1109681

Diagnostic efficacy of sonographic measurement of laryngeal air column width difference for predicting the risk of post-extubation stridor: A meta-analysis of observational studies

Wen-Wen Tsai[1†], Kuo-Chuan Hung[2,3†], Yen-Ta Huang[4], Chia-Hung Yu[3], Chien-Hung Lin[3], I-Wen Chen[5*] and Cheuk-Kwan Sun[6,7*]

[1]Department of Education, Chi Mei Medical Center, Tainan City, Taiwan, [2]School of Medicine, College of Medicine, National Sun Yat-sen University, Kaohsiung City, Taiwan, [3]Department of Anesthesiology, Chi Mei Medical Center, Tainan City, Taiwan, [4]Department of Surgery, College of Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan City, Taiwan, [5]Department of Anesthesiology, Chi Mei Medical Center, Liouying, Tainan City, Taiwan, [6]Department of Emergency Medicine, E-Da Hospital, I-Shou University, Kaohsiung City, Taiwan, [7]School of Medicine for International Students, College of Medicine, I-Shou University, Kaohsiung City, Taiwan

Background: This meta-analysis aimed at assessing the diagnostic accuracy of ultrasound-measured laryngeal air column width difference (ACWD) in predicting post-extubation stridor (PES) in intubated adult patients.

Methods: We searched the Medline, Cochrane Library, EMBASE, and Google scholar databases from inception to October, 2022 to identify studies that examined the diagnostic accuracy of ACWD for PES. The primary outcome was the diagnostic performance by calculating the pooled sensitivity, specificity, and area under the curve (AUC). The secondary outcomes were the differences in ACWD and duration of intubation between patients with and without PES.

Results: Following literature search, 11 prospective studies (intensive care setting, n = 10; operating room setting, n = 1) involving 1,322 extubations were included. The incidence of PES among the studies was 4–25%. All studies were mixed-gender (females: 24.1–68.5%) with sample sizes ranging between 41 and 432. The cut-off values of ACWD for prediction of PES varied from 0.45 to 1.6 mm. The pooled sensitivity and specificity of ACWD for PES were 0.8 (95% CI = 0.69–0.88, I^2: 37.26%, eight studies) and 0.81 (95% CI = 0.72–0.88, I^2: 89.51%, eight studies), respectively. The pooled AUC was 0.87 (95% CI = 0.84–0.90). Patients with PES had a smaller ACWD compared to those without PES (mean difference = −0.54, 95% CI = −0.79 to −0.28, I^2: 97%, eight studies). Moreover, patients with PES had a longer duration of tracheal intubation than that in those without (mean difference = 2.75 days, 95% CI = 0.92, 4.57, I^2: 90%, seven studies).

Conclusion: Ultrasound-measured laryngeal ACWD showed satisfactory sensitivity and specificity for predicting PES. Because of the limited number of studies available, further investigations are needed to support our findings.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42022375772.

KEYWORDS

air column width difference, post-extubation stridor, tracheal extubation, ultrasound, meta-analysis

1. Introduction

Endotracheal intubation is one of the most crucial life-saving procedures to support the respiratory system for critically ill patients on ventilators. Airway complications can, however, arise from tracheal intubation. Although intubation-related airway complications are usually mild in the operating room setting in which the patients receive a short-term intubation (1), prolonged intubation can cause laryngeal edema, increased airflow resistance, and partial airway obstruction that could contribute to post-extubation stridor (PES) (2–4). The development of PES, which occurs in 1.5–26.3% of patients in the critical care setting (4–6), is likely to be associated with an increased risk of respiratory failure and reintubation (6, 7), which is associated with prolonged intensive care unit (ICU) stay, morbidity, and mortality (5).

Recent studies have examined the use of ultrasound-guided techniques, which allows visualization of vocal cords and larynx, to assess airway patency (8–11). The laryngeal air column width, which refers to the width of the acoustic shadow at the level of the vocal cords, can be measured with ultrasonography (12). The laryngeal air column width difference (ACWD), which is defined as the difference in width of the air column between balloon cuff inflation and deflation, has been reported to be a tool for predicting PES (4). Previous studies have demonstrated a significantly smaller ACWD in patients with PES compared to those without (13, 14). Nevertheless, the estimated sensitivity and specificity for predicting PES varied widely among the literature, namely, 50–97% and 57–90%, respectively (9, 13, 14), suggesting notable discrepancy in technical skills involved in the ultrasound assessment of laryngeal edema. Taking into account the lack of evidence addressing this issue, this meta-analysis aimed primarily at investigating the pooled diagnostic efficacy [i.e., pooled sensitivity, specificity, and data derived from the area under receiver operating characteristic (ROC) curve] associated with the use of ultrasound ACWD measurement for predicting PES in intubated patients with planned extubation. We also compared the ACWD and duration of tracheal intubation between patients with and those without PES (i.e., secondary outcomes).

2. Materials and methods

2.1. Study protocol

This systematic review, which followed the preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA) guideline, was registered at PROSPERO (CRD42022375772).

2.2. Data source and literature search

Two authors independently searched the databases including Medline, Cochrane library, Embase, and Google scholar to identify eligible studies focusing on sonographic measurement of ACWD in the prediction of PES from inception to 14, November, 2022, without language restriction. The following keywords were used for literature search: ("Post-extubation" or "Tracheal extubation" or "Airway extubation*" or "Intratracheal extubation*" or "Endotracheal extubation*") and ("Ultrasound" or "Ultrasonography" or "Ultrasound-guided" or "Sonography" or "Echography" or "Echotomography" or "Ultrasonic"" or "Laryngeal ACWD") and ("Stridor" or "Airway edema" or "Airway obstruction" or "subglottic stenosis" or "Laryngeal edema"). Manual searching was also performed for discovering potentially relevant studies. Conflicts between authors were solved by consensus that involved a third investigator. The search detail for one of the databases (i.e., Medline) is shown in **Supplementary Table 1**.

2.3. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (a) adult patients in whom tracheal extubation was attempted in the critical care setting or operating room setting; (b) sonographic measurement of ACWD was used to predict laryngeal edema or PES regardless of cut-off value. The criteria for the diagnosis of laryngeal edema/PES were based on those of individual studies; (c) availability of details regarding sensitivity, specificity, number of patients with or without PES, and the value of ACWD. For the current meta-analysis, randomized control trial, cohort study, and case-control study were all considered eligible for inclusion.

Excluded studies were (a) those reported as abstracts, conference papers, case reports, case series, or review articles; (b) those focused on the pediatric population; (c) those without outcomes of interest; (d) those with no available full text; or (e) those that involved the combination of different tests to predict PES.

2.4. Data extraction

Data was independently extracted from the individual studies by two authors. Disagreements were resolved by a third investigator. The following data were collected: first author's name, study characteristics (e.g., sample size, setting), patient's age, gender, sensitivity, specificity, value of ACWD, duration of tracheal

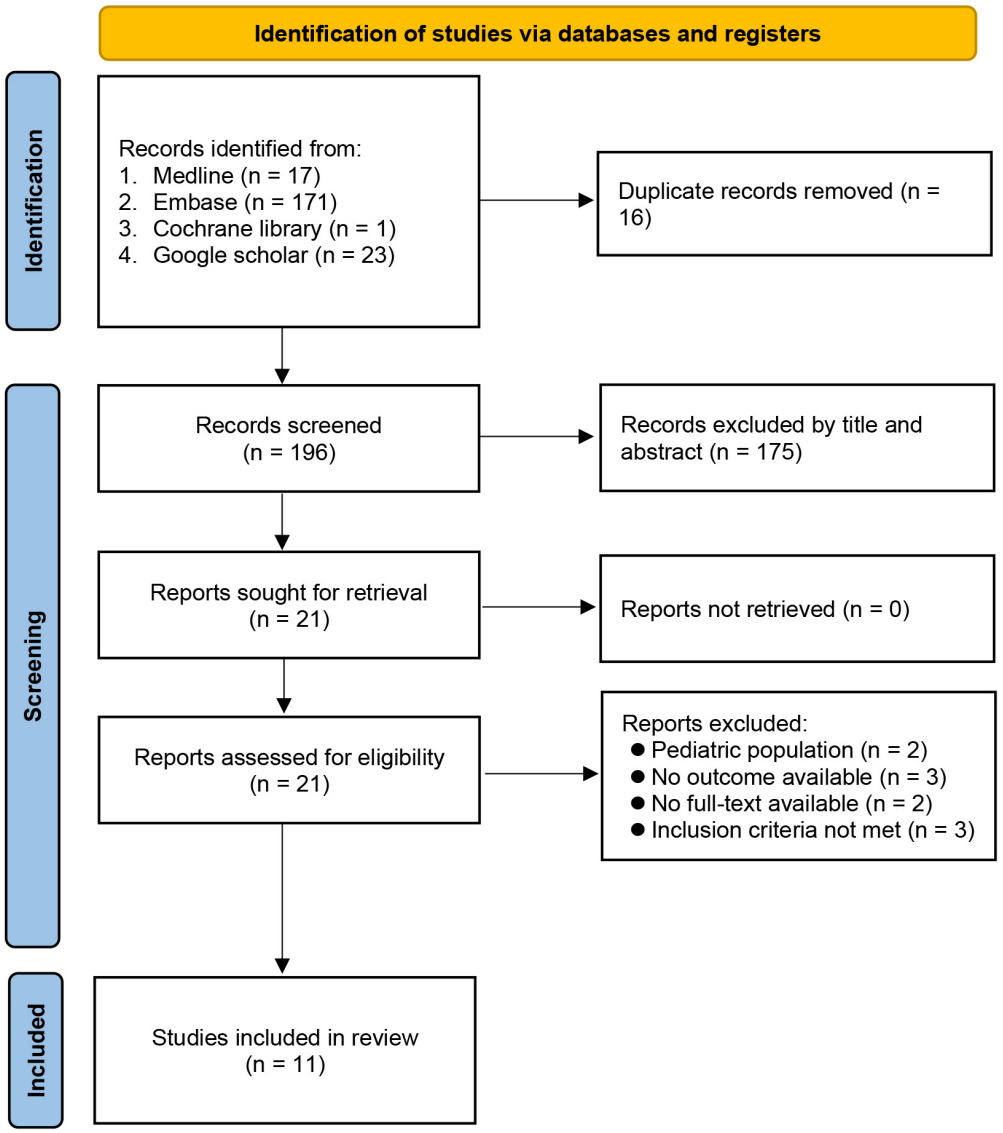


FIGURE 1
PRISMA flow diagram of study selection for the current meta-analysis.

intubation, incidence of PES, and country. If different cut-off values of ACWD were used to predict PES in one study, we extracted the dataset with the highest area under the curve (AUC) available. For missing information, we tried to contact the authors of the articles.

2.5. Outcomes and definitions

The main outcome was the diagnostic efficacy of sonographic measurement of ACWD in predicting PES. The pooled sensitivity, specificity, and ROC were used to assess the diagnostic efficacy regardless of the threshold used. The secondary outcomes included the differences in ACWD and the duration of tracheal intubation between patients with and those without PES. ACWD was defined as the use of ultrasound to measure ACWD between the inflated and deflated cuffs regardless of the manufacturer of the ultrasound equipment. The diagnostic criteria of PES were in accordance with those of individual studies.

2.6. Quality assessment

The quality of each included study was evaluated using the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool that comprises two categories, namely, "risk of bias" and "applicability concerns." While the former contains four domains, the latter consists of three domains for quality assessment (15). Two authors subjectively reviewed all the included studies and rated each domain as "low risk," "some concerns," or "high risk." Disagreements were resolved through discussion till a consensus was reached. A third author was involved if necessary.

2.7. Statistical analysis

The association of PES with ACWD and the duration of intubation was analyzed by using a random effects model with Review Manager version 5.3. We calculated the pooled estimates of sensitivity

10.3389/fmed.2023.1109681

TABLE 1 Characteristics of studies ($n = 11$).

References	Number of patients	Female (%)	Mean age (year)[§]	Setting	ACWD (mm)[§]	Cut-off value (mm)	Duration of intubation (days)[§]	PES (%)	Country
Abd Elghafar et al. (18)	70	35.7	39 vs. 38	ICU	1.14 ± 0.70 vs. 1.78 ± 0.53	1.5	7.78 vs. 4.25	12.9	Egypt
Bhargava et al. (19)	200	68.5	46 vs. 45	OR	0.13 ± 0.03 vs. 0.29 ± 0.026	1	140 vs. 130[‡]	6	India
El-Baradey et al. (9)	432	26.9	25.4 vs. 47.3	ICU	0.6 ± 0.5 vs. 1.9 ± 0.7	0.9	14.3 vs. 9.6	10.4	Egypt
Hasan and Ahmed (20)	58	24.1	53.1 vs. 55.2	ICU	0.56 ± 0.07 vs. 0.86 ± 0.5	NA	7.23 vs. 6.53	12.1	Egypt
Mikaeili et al. (13)	41	36.6	57.2[¶]	ICU	NA	0.85	At least 24 h	9.8	Iran
Mohammed et al. (14)	167	37.7	59.5 vs. 56.2	ICU	0.541 ± 0.33 vs. 1.237 ± 0.44	0.65	10.6 vs. 5.9	10.2	Egypt
Patel et al. (21)	51	41.2	NA[†]	ICU	0.4 ± 0.2 vs. 0.8 ± 0.7	0.45	3.5 vs. 3.9	4	USA
Sahbal et al. (22)	50	38.0	NA	ICU	0.95 ± 0.08 vs. 0.97 ± 0.09	0.905	At least 24 h	8	Egypt
Sutherasan et al. (23)	101	38.6	72.2 vs. 66.9	ICU	1.08 ± 0.81 vs. 1.99 ± 0.79	1.6	7.9 vs. 6.2	16.8	Thailand
Venkategowda et al. (24)	72	48.6	54 vs. 55	ICU	NA	NA	5.6 vs. 3.9	6.9	India
Zytoun et al. (25)	80	42.5	46.4[¶]	ICU	NA	0.9	40% vs. 55%[#]	25	Egypt

Operating room (total thyroidectomy); PES, post-extubation stridor; [¶]overall population; [†]<45 y/o: $n = 13$; 45–54 y/o: $n = 13$; > 55 y/o: $n = 25$; [§]presented as PES vs. non-PES; ACWD, air column width difference; [‡]minutes; NA, not available; [#]proportion of patients (PES vs. non-PES) with duration of tracheal intubation ≥5 days.

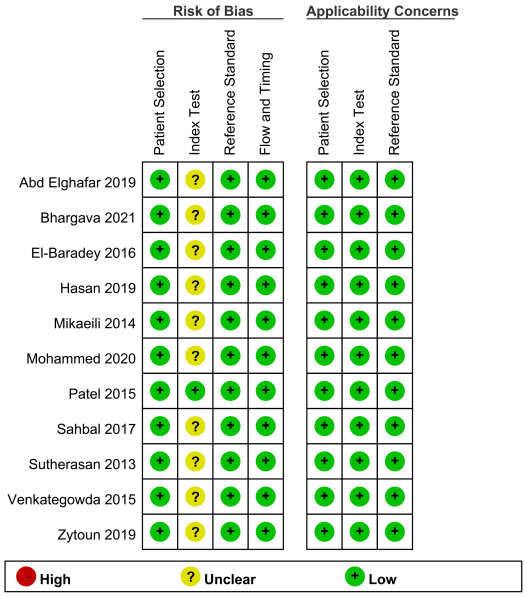


FIGURE 2
Risk of bias and applicability concerns.

and specificity as well as the positive and negative likelihood ratios [LR (+) and LR (−)], which were acquired with the formulas: LR (+) = sensitivity/(1−specificity); LR (−) = (1−sensitivity)/specificity. While statistical heterogeneity was investigated using Cochran Q-statistics, heterogeneity between studies was evaluated with the random effects model using the I^2 statistics. The diagnostic performance of sonography was assessed with AUC from constructed summary ROC (sROC) curves (16). Based on LR (+) and LR (−), post-test probability was estimated with a Fagan's nomogram. The potential publication bias was examined by inspecting Deek's funnel plot. A $p < 0.05$ was regarded as statistically significant. Forest plots of pooled estimates of sensitivity and specificity, Deek's funnel plot, sROC curve, and Fangan's nomogram plot were constructed with the meta-analytical integration of diagnostic test accuracy studies (MIDAS) command in Stata 15 (StataCorp LLC., College Station, TX, USA) as previously reported (17).

3. Results

3.1. Selection and characteristics of studies

A literature search identified 212 potentially eligible articles. After article review, 16 duplicates were removed. Of the remaining 196 articles screened based on title and abstract, 175 were excluded. After eliminating 10 more articles according to our exclusion criteria, 11 studies involving 1,322 participants were included for the current analysis (9, 13, 14, 18–25) (**Figure 1**). The characteristics of the included studies published between 2013 and 2021 are shown in **Table 1**. Of the 11 studies, eight provided details for the calculation of sensitivity and specificity (9, 13, 14, 18, 19, 22, 23, 25). Eight (9, 14, 18–23) and seven studies (9, 14, 18, 20, 21, 23, 24) were available for analysis of the association of PES with ACWD and the duration of intubation, respectively. Most studies (i.e., 10) were conducted

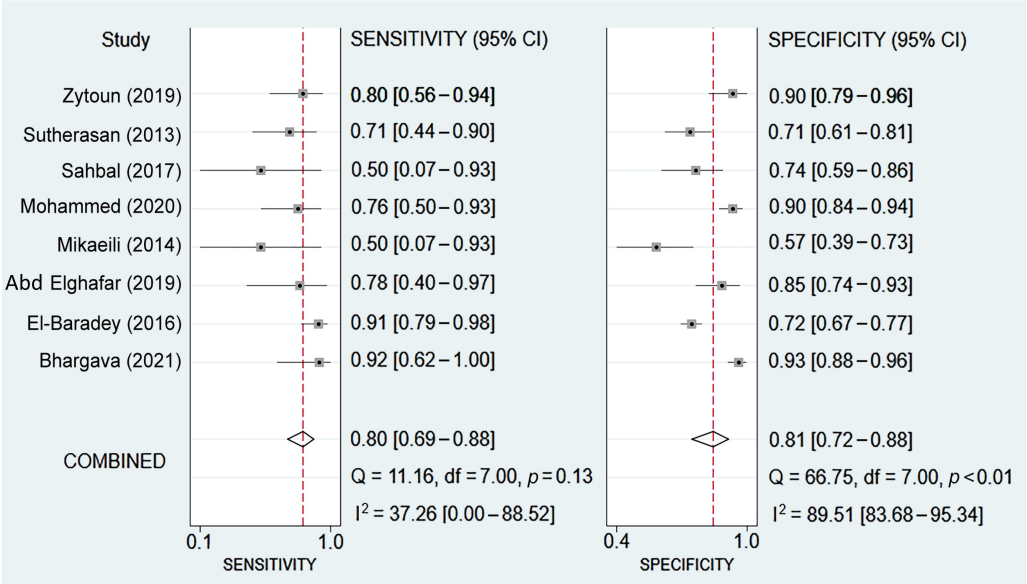


FIGURE 3
Forest plot showing the pooled sensitivity and specificity of sonography-measured air column width difference (ACWD) in predicting post-extubation stridor (PES).

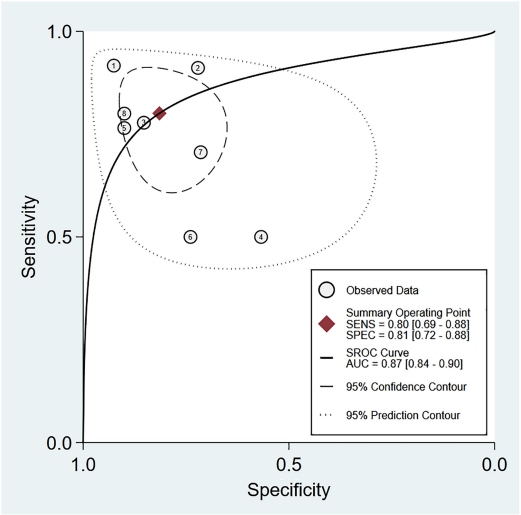


FIGURE 4
Summary receiver operating characteristic (sROC) curve analysis of sensitivity and specificity of air column width difference (ACWD) for predicting post-extubation stridor (PES). Weighted sROC is shown as a solid line. Open circles denote estimates of sensitivity and (1−specificity) of individual studies. Diamonds represent pooled point estimates of outcomes. AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

prospectively in the intensive care unit setting (9, 13, 14, 18, 20–25) and one was performed in the operating room setting (19). All studies were mixed-gender (females: 24.1–68.5%) with sample sizes ranging from 41 to 432. The cut-off values of ACWD for the prediction of PES were available in nine studies (range, 0.45–1.6 mm). The incidence of PES was 4–25%. Six studies were conducted in Egypt (9, 14, 18, 20, 22, 25), two in India (19, 24), one each in the USA (21), Thailand (23), and Iran (13).

The risk of bias and applicability concerns in all studies are shown in Figure 2. Regarding the risk of bias, the domains of patient selection, reference standard, flow, and timing were considered low in all studies. However, the risk of bias on the domain of index test was deemed unclear in 10 of the studies due to their lack of a pre-defined cut-off value of ACWD. For the applicability concerns, all studies are considered at low risk of bias.

3.2. Diagnostic efficacy of ultrasonography for prediction of post-extubation stridor

Eight studies were available for the calculation of the sensitivity and specificity (9, 13, 14, 18, 19, 22, 23, 25). Relevant data and the definitions of PES are summarized in Supplementary Table 2 and Supplementary Table 3, respectively. The pooled sensitivity and specificity were 0.8 (95% CI = 0.69–0.88, I^2: 37.26%) and 0.81 (95% CI = 0.72–0.88, I^2: 89.51%), respectively (Figure 3). The pooled AUC was 0.87 (95% CI = 0.84–0.90) (Figure 4). LR (+) and LR (−) were 4 and 0.24, respectively (Figure 5). The Fagan plot is shown in Figure 5. The Deek's funnel plot asymmetry test showed a low risk of publication bias (p = 0.26; Figure 6).

3.3. The differences in air column width difference and duration of tracheal intubation in patients with and without post-extubation stridor

Eight studies including 1,129 participants were available for the analysis of ACWD between patients with and those without PES (9, 14, 18–23). By adopting a random-effects model, patients with PES had a smaller ACWD compared to those without PES

(mean difference = −0.54, 95% CI = −0.79 to −0.28, I^2: 97%) (Figure 7). Sensitivity analysis with the leave-one-out method revealed consistent findings in support of the strength of evidence.

Seven studies with 951 participants provided details for the analysis of the association between the duration of tracheal intubation and PES (9, 14, 18, 20, 21, 23, 24). With a random-effects model, patients with PES showed a longer duration of tracheal intubation compared to those without (mean difference = 2.75 days, 95% CI = 0.92, 4.57, I^2: 90%) (Figure 8). Sensitivity analysis demonstrated robustness of the finding.

4. Discussion

The negative impact of extubation failure and reintubation on prognostic outcomes (e.g., prolonged intensive care unit stay) in critically ill patients has underscored the importance of identifying those at high risks of PES (6). Our findings not only demonstrated a lower ACWD values (mean difference = −0.50) in patients with PES but also showed a favorable sensitivity (i.e., 80%) and specificity (i.e., 81%) of using ACWD as a predictor of this complication with an AUC of 0.87. In view of the simplicity of the technique, our results suggested the feasibility of using ACWD as a guidance to determine the suitability of extubation to enhance patient safety in the critical and post-operative care settings.

Although recent advances in critical care technology have significantly improved the prognosis and survival of patients receiving ventilator support (26), extubation failure still occurs in approximately 10–15% of patients (27). Previous studies have shown that extubation failure may be associated with higher rates of tracheotomies, increased mortality, prolonged stay in the intensive care unit, and impaired functional outcome after recovery (28–30). Therefore, avoidance of premature tracheal extubation plays a vital role in the delivery of critical care. On the other hand, delay in weaning from mechanical ventilation could contribute to complications such as nosocomial infections, ventilator-induced lung injury, and delirium (31, 32). In addition, prolonged mechanical ventilation imposes a heavy financial burden in the intensive care unit setting (33). Laryngeal edema, which often manifests with stridor after tracheal extubation, is one of the most important contributors to extubation failure in the critical care setting (34). In fact, a previous study attributed failed extubation to the presence of laryngeal edema in up to 38% of all cases (35). To avoid premature or delayed tracheal extubation, a diagnostic technique that can reliably predict laryngeal edema or PES with high sensitivity and specificity is needed.

Although previous investigations have identified a number of potential risk factors for PES, including the female gender, difficult or prolonged intubation, use of large-sized endotracheal tubes, and a high cuff pressure (7, 36–39), such predictors are too non-specific to predict the occurrence of laryngeal edema and/or stridor in the real-world clinical scenario. In contrast, one of the well-defined techniques to predict the absence of post-extubation laryngeal edema was the cuff leak test (7, 40, 41). Despite the recommendation of performing a cuff leak test among mechanically ventilated adults with a high risk of PES by the American Thoracic Society and American College of Chest Physicians (42), a previous meta-analysis involving 28 studies with 4,493 extubations revealed a sensitivity and specificity of cuff leak test for predicting the absence of laryngeal edema of only 0.62 and 0.87, respectively. The low sensitivity raised a concern that this test may mislead clinicians to believe in the presence of laryngeal edema that unnecessarily prolonged mechanical ventilation (6). In addition, although the cuff leak test is supposed to be performed when the patient is well sedated with full mechanical ventilatory support, its accuracy may be impaired in real-world practice that involves patients who are being weaned from mechanical ventilation (e.g., on pressure support ventilation or spontaneous breathing trial) (23). Furthermore, apart from the space between the tracheal wall and the cuff after endotracheal cuff deflation, the accuracy of the cuff leak test also depend on other factors such as the expiratory tracheal airflow, expiratory time, and air trapping from collapsing airway related to chronic obstructive pulmonary disease (43, 44).

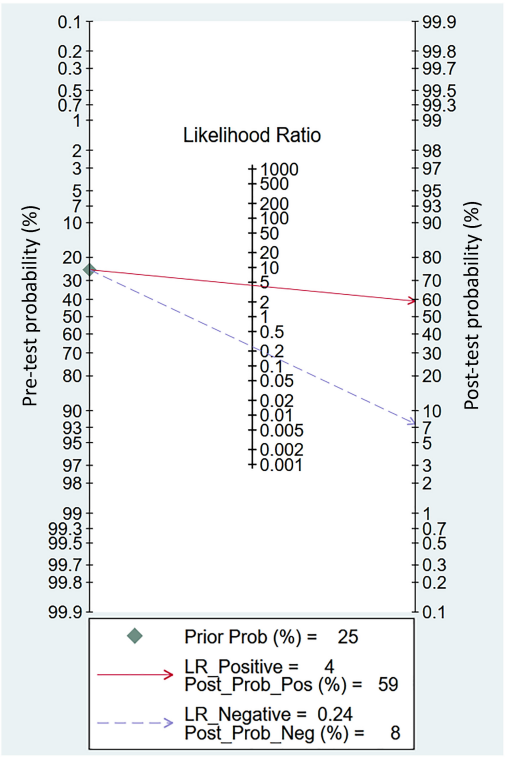


FIGURE 5
Fagan's nomogram plot for assessing clinical utility of sonography-measured air column width difference (ACWD) in post-extubation stridor (PES) prediction. LR, likelihood ratio; Prob, probability; Pos, positive; Neg, negative.

In the current meta-analysis, the pooled sensitivity and specificity of sonography-guide ACWD technique for predicting PES were 0.8 and 0.81, respectively, supporting the feasibility of this technique in the critical care setting. Moreover, in contrast to the cuff leak test that requires mechanical ventilation, the ACWD approach only involves sonographic measurement that is more practical in the intensive care unit (45). Besides, previous studies have reported additional merits of the ACWD technique including safety, ease of image acquisition because of conspicuous landmarks (i.e., cricoid and thyroid cartilage) even in obese individuals as well as the short distance between the skin to vocal cords (23). The additional advantage is the simplicity of interpretation with a larger ACWD representing a lower chance of laryngeal edema (23). In the current meta-analysis, the value of ACWD was lower in patients with PES compared to those without, further validating the theory of its operation. The high heterogeneity in this outcome may be attributed to the variations

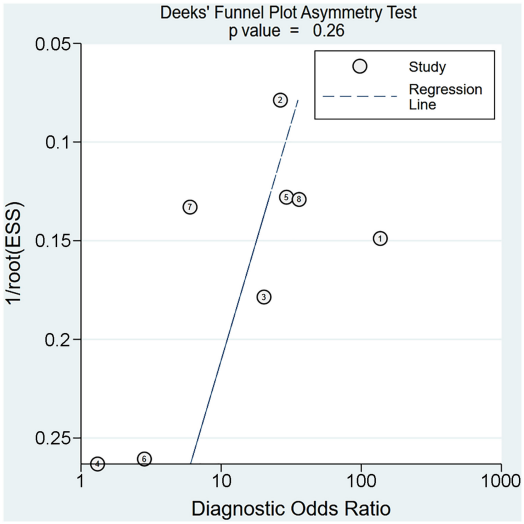


FIGURE 6
Deek's funnel plot asymmetry test for assessment of publication bias across the included studies.

in intubation duration, size of tracheal tube, patient gender, and the operator's experience.

Our results showed an incidence of PES ranging from 4 to 25%, which is consistent with the findings of previous studies that reported an estimated PES incidence of 1.5–26.3% in the critical care setting (4–6). Regarding the duration of intubation, the present study demonstrated a longer intubation time in patients with PES compared to those without. The finding supported a positive association of prolonged intubation with the risk of PES as previously reported (5). One of our included studies that focused on patients receiving total thyroidectomy in the operating room setting revealed an incidence of PES up to 6% (19), highlighting that even short-term tracheal intubation (e.g., 130–140 min) may cause PES in the operating room setting. Accordingly, the use of sonography-measured ACWD may also be recommended for those undergoing head and neck surgeries before extubation regardless of the duration of intubation to enhance patient safety.

There were several limitations in the current meta-analysis. First, the absence of standardized methods to assess the severity of laryngeal edema (4) across our included studies may bias our findings. Similarly, the definition of PES used in the studies may have varied and blinding of assessment may not have been adequate in individual studies. Second, although a previous meta-analysis reported that the pooled sensitivity and specificity of the cuff leak test for reintubation rate were 0.66 and 0.88, respectively (34), we did not assess the impact of sonography-measured ACWD on the reintubation rate because of a lack of relevant information. Third, the focus of most of our included studies on patients in the intensive care unit may restrict the applicability of our findings in other clinical settings. In addition, our inclusion of only adult patients may not justify the extrapolation of our results to the pediatric population. Fourth, the effects of other potential confounders (e.g., size of tracheal tube or gender) that may influence the accuracy of sonography-measured ACWD were not investigated in the present study because of limited data availability. Fifth, the application of steroids, which was noted in over one-fourth of patients (25.5%, n = 13) within 24 h of endotracheal extubation in one of the included studies (21), may impede the evaluation of the diagnostic accuracy of ACWD for PES. Finally, potential variations in calibration and image quality

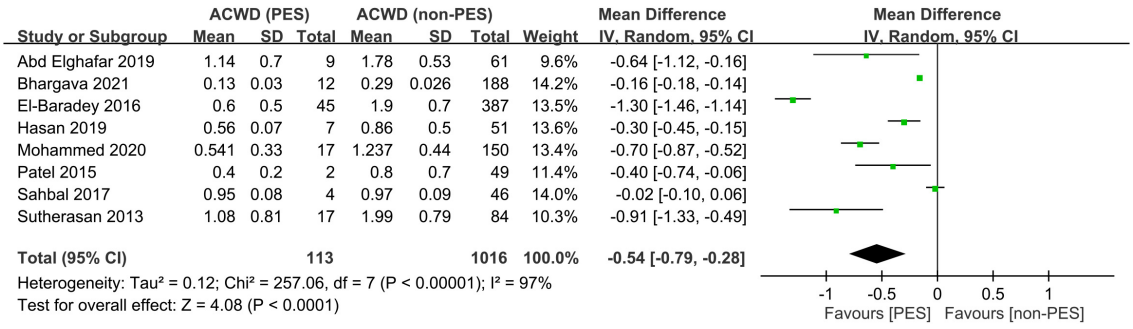


FIGURE 7
Forest plot comparing the air column width difference (ACWD) between patients with and without post-extubation stridor (PES). CI, confidence interval.

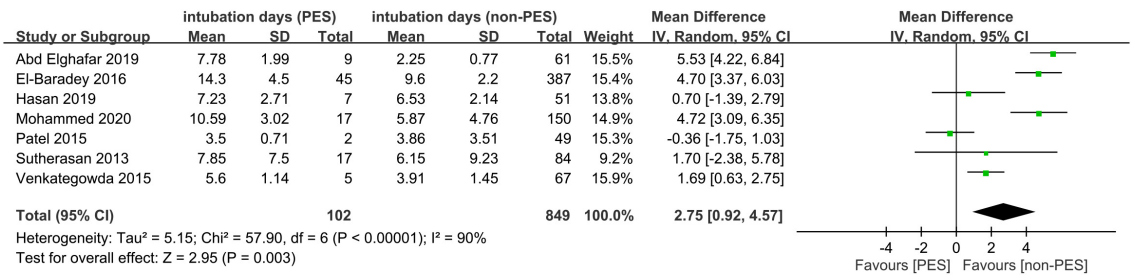


FIGURE 8
Forest plot comparing intubation time between patients with and without post-extubation stridor (PES). CI, confidence interval.

of ultrasound machines from different manufacturers, operator's experience, as well as the head and neck position (e.g., flexion, extension) of the patient may influence distance measurement with the technique (23). Therefore, further investigations are warranted to address these issues.

5. Conclusion

Our results demonstrated that the measurement of laryngeal ACWD with ultrasound may be a clinically useful tool in the assessment of laryngeal edema or the prediction of PES. The favorable sensitivity and specificity may support its routine use in patients at high risk of PES. Nevertheless, the use of this technique does not obviate the need for close patient monitoring to ensure the absence of post-extubation complications. Further multicenter studies with standardized definitions and cutoffs, ideally paired with an intervention, are necessary to define the role of ACWD in routine clinical practice.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

W-WT and K-CH: conceptualization. Y-TH: methodology and software. C-HY and K-CH: validation. K-CH and Y-TH: formal analysis. C-HL and W-WT: investigation. I-WC: resources. I-WC and K-CH: data curation. K-CH, W-WT, I-WC, and C-KS: writing—original draft preparation. K-CH, I-WC, and C-KS: writing—review and editing. C-KS: visualization and supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1109681/full#supplementary-material

References

1. Brodsky M, Akst L, Jedlanek E, Pandian V, Blackford B, Price C, et al. Laryngeal injury and upper airway symptoms after endotracheal intubation during surgery: a systematic review and meta-analysis. *Anesthesia Analgesia.* (2021) 132:1023–32. doi: 10.1213/ANE.0000000000005276

2. Shinn J, Kimura K, Campbell B, Sun Lowery A, Wootten C, Garrett C, et al. Incidence and outcomes of acute laryngeal injury after prolonged mechanical ventilation. *Crit Care Med.* (2019) 47:1699–706.

3. Benjamin B. Prolonged intubation injuries of the larynx: endoscopic diagnosis, classification, and treatment. *Annals Otol Rhinol Laryngol.* (2018) 127:492–507.

4. Pluijms W, van Mook W, Wittekamp B, Bergmans D. Postextubation laryngeal edema and stridor resulting in respiratory failure in critically ill adult patients: updated review. *Crit Care (London, England).* (2015) 19:295. doi: 10.1186/s13054-015-1018-2

5. Tanaka A, Uchiyama A, Horiguchi Y, Higeno R, Sakaguchi R, Koyama Y, et al. Predictors of post-extubation stridor in patients on mechanical ventilation: a prospective observational study. *Sci Rep.* (2021) 11:19993. doi: 10.1038/s41598-021-99501-8

6. Schnell D, Planquette B, Berger A, Merceron S, Mayaux J, Strasbach L, et al. Cuff Leak test for the diagnosis of post-extubation stridor: a multicenter evaluation study. *J Intens Care Med.* (2019) 34:391–6. doi: 10.1177/0885066617700095

7. Jaber S, Chanques G, Matecki S, Ramonatxo M, Vergne C, Souche B, et al. Post-extubation stridor in intensive care unit patients. risk factors evaluation and importance of the cuff-leak test. *Intens Care Med.* (2003) 29:69–74. doi: 10.1007/s00134-002-1563-4

8. El Amrousy D, Elkashlan M, Elshmaa N, Ragab A. Ultrasound-Guided laryngeal air column width difference as a new predictor for postextubation stridor in children. *Crit Care Med.* (2018) 46:e496–501. doi: 10.1097/CCM.0000000000003068

9. El-Baradey G, El-Shmaa N, Elsharawy F. Ultrasound-guided laryngeal air column width difference and the cuff leak volume in predicting the effectiveness of steroid therapy on postextubation stridor in adult. are they useful? *J Crit Care.* (2016) 36:272–6. doi: 10.1016/j.jcrc.2016.07.007

10. Fiorelli A, Messina G, Bove M, Natale G, Noro A, Cascone R, et al. Ultrasound for assessment and follow-up of airway stenosis. *Ann Thoracic Surg.* (2022) 113:1624–33.

11. Aldriweesh B, Khan A, Aljasser A, Bukhari M, Alrabiah A, AlAmmar A. Correlation of airway ultrasonography and laryngoscopy findings in adults with subglottic stenosis: a pilot study. *Eur Arch Oto-rhino-laryngol.* (2022) 279:1989–94. doi: 10.1007/s00405-021-07195-5

12. Ding L, Wang H, Wu H, Chang C, Yang P. Laryngeal ultrasound: a useful method in predicting post-extubation stridor. a pilot study. *Eur Respirat J.* (2006) 27:384–9. doi: 10.1183/09031936.06.00029605

13. Mikaeili H, Yazdchi M, Tarzamni M, Ansarin K, Ghasemzadeh M. Laryngeal ultrasonography versus cuff leak test in predicting postextubation stridor. *J Cardiov Thoracic Res.* (2014) 6:25. doi: 10.5681/jcvtr.2014.005

14. Mohammed A, Shaaban L, El-Malah H, Gad S, Hashem M. Laryngeal ultrasound as a bedside tool in detecting postextubation stridor in patients with respiratory illness. *J Curr Med Res Practice.* (2020) 5:36.

15. Whiting P, Rutjes A, Westwood M, Mallett S, Deeks J, Reitsma J, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Int Med.* (2011) 155:529–36.

16. Moses L, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Statis Med.* (1993) 12:1293–316. doi: 10.1002/sim.4780121403

17. Hung K, Huang Y, Kuo J, Hsu C, Yew M, Chen J, et al. Elevated surgical pleth index at the end of surgery is associated with postoperative moderate-to-severe pain: a systematic review and meta-analysis. *Diagnostics (Basel, Switzerland).* (2022) 12:2167. doi: 10.3390/diagnostics12092167

18. Abd Elghafar M, Nassar W, Altomey M. The benefit of laryngeal ultrasound in ICU: prediction of postextubation stridor in patients undergoing mechanical ventilation. *EJICT.* (2019) 7:20–7.

19. Bhargava T, Kumar A, Bharti A, Khuba S. Comparison of laryngeal ultrasound and cuff leak test to predict post-extubation stridor in total thyroidectomy. *Turk Anestezi Reanim.* (2021) 49:238–43. doi: 10.5152/TJAR.2020.176

20. Hasan A, Ahmed F. Predictive value of cuff leak test, laryngeal ultrasound, and fiberoptic laryngoscopy for postextubation stridor after prolonged intubation. *Res Opin Anesthesia Intens Care.* (2019) 6:355.

21. Patel A, Ani C, Feeney C. Cuff leak test and laryngeal survey for predicting post-extubation stridor. *Ind J.* (2015) 59:96–102. doi: 10.4103/0019-5049.151371

22. Sahbal M, Mohamed K, Zaghla H, Kenawy M. Laryngeal ultrasound versus cuff leak test in prediction of post-extubation stridor. *Egypt J Crit Care Med.* (2017) 5:83–6.

23. Sutherasan Y, Theerawit P, Hongphanut T, Kiatboonsri C, Kiatboonsri S. Predicting laryngeal edema in intubated patients by portable intensive care unit ultrasound. *J Crit Care.* (2013) 28:675–80. doi: 10.1016/j.jcrc.2013.05.011

24. Venkategowda P, Mahendrakar K, Manimala Rao S, Mutkule D, Shirodkar C, Yogesh H. Laryngeal air column width ratio in predicting post extubation stridor. *Ind J Crit Care Med.* (2015) 19:170–3.

25. Zytoun T, Noeman Y, Abdelhady M, Waly A. The role of laryngeal ultrasound in predicting postextubation laryngeal edema. *Res Opin Anesthesia Intens Care.* (2019) 6:294.

26. Schweickert W, Pohlman M, Pohlman A, Nigos C, Pawlik A, Esbrook C, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet (London, England).* (2009) 373:1874–82.

27. Fernando S, Tran A, Sadeghirad B, Burns K, Fan E, Brodie D, et al. Noninvasive respiratory support following extubation in critically ill adults: a systematic review and network meta-analysis. *Intens Care Med.* (2022) 48:137–47.

28. Thille A, Boissier F, Ben Ghezala H, Razazi K, Mekontso-Dessap A, Brun-Buisson C. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. *Crit Care Med.* (2015) 43:613–20. doi: 10.1097/CCM.0000000000000748

29. Rishi M, Kashyap R, Wilson G, Schenck L, Hocker S. Association of extubation failure and functional outcomes in patients with acute neurologic illness. *Neurocrit Care.* (2016) 24:217–25.

30. Zhao Q, Wang H, Luo J, Luo M, Liu L, Yu S, et al. Development and validation of a machine-learning model for prediction of extubation failure in intensive care units. *Front Med.* (2021) 8:676343. doi: 10.3389/fmed.2021.676343

31. Klompas M. Complications of mechanical ventilation–the CDC's new surveillance paradigm. *New Engl J Med.* (2013) 368:1472–5. doi: 10.1056/NEJMp1300633

32. Zaal I, Devlin J, Peelen L, Slooter AJA. systematic review of risk factors for delirium in the ICU. *Crit Care Med.* (2015) 43:40–7.

33. Dasta J, McLaughlin T, Mody S, Piech C. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med.* (2005) 33:1266–71.

34. Kuriyama A, Jackson J, Kamei J. Performance of the cuff leak test in adults in predicting post-extubation airway complications: a systematic review and meta-analysis. *Crit Care (London, England).* (2020) 24:640. doi: 10.1186/s13054-020-03358-8

35. Daley B, Garcia-Perez F, Ross S. Reintubation as an outcome predictor in trauma patients. *Chest.* (1996) 110:1577–80.

36. Cheng K, Chen C, Tan C, Chen H, Lu C, Zhang H. Methylprednisolone reduces the rates of postextubation stridor and reintubation associated with attenuated cytokine responses in critically ill patients. *Minerva Anestesiol.* (2011) 77:503–9.

37. Sandhu R, Pasquale M, Miller K, Wasser T. Measurement of endotracheal tube cuff leak to predict postextubation stridor and need for reintubation. *J Am College Surgeons.* (2000) 190:682–7. doi: 10.1016/s1072-7515(00)00269-6

38. Erginel S, Ucgun I, Yildirim H, Metintas M, Parspour S. High body mass index and long duration of intubation increase post-extubation stridor in patients with mechanical ventilation. *Tohoku J Exp Med.* (2005) 207:125–32. doi: 10.1620/tjem.207.125

39. Mehel D, Özdemir D, Çelebi M, Aydemir S, Akgül G, Özgür A. Classification of laryngeal injury in patients with prolonged intubation and to determine the factors that cause the injury. *Am J Otolaryngol.* (2020) 41:102432.

40. De Bast Y, De Backer D, Moraine J, Lemaire M, Vandenborght C, Vincent J. The cuff leak test to predict failure of tracheal extubation for laryngeal edema. *Intens Care Med.* (2002) 28:1267–72.

41. Kallet R, Matsushima A, Yoo S, Lipnick M. Utilization of a risk stratification tool and volume-based cuff leak test to assess post-extubation stridor. *Respiratory Care* (2022). [Epub ahead of print]. doi: 10.4187/respcare.10285

42. Girard T, Alhazzani W, Kress J, Ouellette D, Schmidt G, Truwit J, et al. An official American thoracic society/American college of chest physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. *Am J Respirat Crit Care Med.* (2017) 195:120–33. doi: 10.1164/rccm.201610-2075ST

43. Prinianakis G, Alexopoulou C, Mamidakis E, Kondili E, Georgopoulos D. Determinants of the cuff-leak test: a physiological study. *Crit Care (London, England).* (2005) 9:R24–31. doi: 10.1186/cc3012

44. De Backer D. The cuff-leak test: what are we measuring? *Crit Care (London, England).* (2005) 9:31–3.

45. Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein D, Mathis G, Kirkpatrick A, et al. International evidence-based recommendations for point-of-care lung ultrasound. *Intens Care Med.* (2012) 38:577–91.

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 27 April 2023
DOI 10.3389/fmed.2023.1147373

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Oksana B. Stoliar,
Ternopil Volodymyr Hnatyuk National Pedagogical University, Ukraine
Edmund Pool,
University of the Western Cape, South Africa

*CORRESPONDENCE
Virendra Kumar Yadav
✉ yadava94@gmail.com
Biswaranjan Paital
✉ biswaranjanpaital@gmail.com
Dipak Kumar Sahoo
✉ dsahoo@iastate.edu;
✉ dipaksahoo11@gmail.com

RECEIVED 19 January 2023
ACCEPTED 05 April 2023
PUBLISHED 27 April 2023

CITATION
Yadav VK, Choudhary N, Inwati GK, Rai A, Singh B, Solanki B, Paital B and Sahoo DK (2023) Recent trends in the nanozeolites-based oxygen concentrators and their application in respiratory disorders. *Front. Med.* 10:1147373. doi: 10.3389/fmed.2023.1147373

Recent trends in the nanozeolites-based oxygen concentrators and their application in respiratory disorders

Virendra Kumar Yadav[1,2]*, Nisha Choudhary[2,3], Gajendra Kumar Inwati[4], Ashita Rai[5], Bijendra Singh[6], Bharat Solanki[7], Biswaranjan Paital[8]* and Dipak Kumar Sahoo[9]*

[1]Department of Biosciences, School of Liberal Arts and Sciences, Mody University of Science and Technology, Lakshmangarh, Rajasthan, India, [2]Department of Life Sciences, Hemchandracharya North Gujarat University, Patan, Gujarat, India, [3]Department of Environment Sciences, School of Sciences, P P Savani University, Surat, Gujarat, India, [4]Department of Chemistry, Medicaps University, Indore, Madhya Pradesh, India, [5]School of Environment and Sustainable Development, Central University of Gujarat, Gandhinagar, Gujarat, India, [6]School of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat, India, [7]Department of Biochemistry, M B Patel Science College, Anand, Gujarat, India, [8]Redox Regulation Laboratory, Department of Zoology, College of Basic Science and Humanities, Odisha University of Agriculture and Technology, Bhubaneswar, India, [9]Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA, United States

Medical-grade oxygen is the basic need for all medical complications, especially in respiratory-based discomforts. There was a drastic increase in the demand for medical-grade oxygen during the current pandemic. The non-availability of medical-grade oxygen led to several complications, including death. The oxygen concentrator was only the last hope for the patient during COVID-19 pandemic around the globe. The demands also are everlasting during other microbial respiratory infections. The yield of oxygen using conventional molecular zeolites in the traditional oxygen concentrator process is less than the yield noticed when its nano-form is used. Nanotechnology has enlightened hope for the efficient production of oxygen by such oxygen concentrators. Here in the current review work, the authors have highlighted the basic structural features of oxygen concentrators along with the current working principle. Besides, it has been tried to bridge the gap between conventional oxygen concentrators and advanced ones by using nanotechnology. Nanoparticles being usually within 100nm in size have a high surface area to volume ratio, which makes them suitable adsorbents for oxygen. Here authors have suggested the use of nano zeolite in place of molecular zeolites in the oxygen concentrator for efficient delivery of oxygen by the oxygen concentrators.

KEYWORDS

chabazite, microbial infection, molecular sieves, nano-zeolite, oxygen therapy, pneumonia, respiratory disorders

1. Introduction

Oxygen is the basic requirement for both a healthy and a diseased individual. There are certain medical diseases, especially cardiovascular respiratory disorders, where there is a requirement for pure or concentrated oxygen by the patient (1, 2). This pure or concentrated oxygen is indeed known as medical oxygen, and in the absence of it, a patient may experience

hypoxemia [low levels of oxygenated blood (3)]. Hypoxemia is caused by a range of common conditions—including childhood pneumonia, newborn conditions (4, 5), and obstetric emergencies (6, 7). The body of the sufferer will experience severe detrimental consequences from hypoxemia on the cells that carry out crucial biological functions (8). The atmospheric air with a 21% O_2 concentration and when its percentage is below 19.5% by volume and/or highly elevated CO_2 level in air is called an oxygen-deficient condition (9). The O_2 deficient in body a comparatively O_2 less environment can lead to a condition called asphyxiation (10). When severe hypoxemia is not quickly diagnosed and addressed, it can lead to death.

For a healthy individual, 21% of oxygen is sufficient, but for a patient suffering from a respiratory disease or cardiovascular then, there is a requirement for concentrated or pure oxygen or medical grade oxygen. Oxygen is listed as an essential drug in India. If pure oxygen is not provided to the patient on time, during hypoxemia, then the lung will be devoid of oxygenated blood, from where the oxygen will not be supplied to the vital organs of the body (11). As a result, it will lead to damage of organs and, ultimately, the death of the patients. Based on the application, oxygen can be classified into two classes: medical and industrial grade. Medical grade oxygen is highly pure (12) in order to supply concentrated oxygen to the patient, while impurities could be permitted in the industrial grade, which is needed in steel making, etc. Moreover, medical-grade oxygen should be supplied in sterilized cylinders in order to prevent other diseases as per the gas cylinder rule 1981 (13, 14).

For the patient's recovery from several illnesses, including respiratory infections such as asthma, emphysema, and perhaps other severe acute respiratory syndrome (SARS)-coronavirus-2 (CoV2) infestations, supplemental oxygen is recommended (15). Oxygen therapy is provided by means of an oxygen cylinder, oxygen generation plant, and oxygen concentrators. The demand for oxygen concentrators has grown drastically due to the SARS-CoV_2. In order to help patients with lower blood oxygen levels, oxygen concentrators are biomedical equipment that typically concentrates oxygen from the atmosphere (16). Oxygen concentrators have been used for the last several decades, especially in low-income countries, where the medical facility is poorly developed, or in remote or hilly areas where hospitals are very far. Oxygen concentrators could be either fixable or static, or they could be mobile or portable (16).

As the word "*concentrator*" indicates the concentration or enrichment of anything, and here oxygen is being concentrated from the air mixture. So, in layman's language, we can say that this device concentrates oxygen from the air by eliminating nitrogen from them. Our atmospheric air contains a mixture of gases, mainly nitrogen (78%), oxygen (21%), and a small number of other gases. So, the main purpose of this device is to eliminate the nitrogen (which is present in a larger amount) from the air and supply the residual component, i.e., oxygen up to 90% purity, to the patient. When the air is sent through an oxygen concentrator, it is converted to 90–95 percent pure oxygen and 5–10 percent nitrogen. Since it is challenging to obtain that amount of oxygen alone without the aid of medical equipment, the nitrogen is segregated to ensure that patients receive the maximum dose of oxygen available. Home-based oxygen concentrators have numerous advantages compared to oxygen cylinders, which may leak or burst (17). Compared to conventional oxygen cylinders, oxygen concentrators are significantly less hazardous (18). Old-fashioned oxygen cylinders have been replaced with household and transportable oxygen concentrators that can "generate" their own oxygen (19). From time to time, there were several modifications also in the oxygen concentrator; for instance, few investigators used it alone, few used it with other oxygen devices like ventilators (20), and few used nanomaterials in place of micron-sized zeolites to increase the efficiency of the concentrator (21). Molecular zeolites are artificially produced molecular sieves. They are prepared from alkali metal aluminosilicates. They have common applications in the gas chromatography also to sieve the molecules. The calcium aluminosilicate has pore diameter of 0.5 nm, while sodium aluminosilicate has pore diameter of 1 nm. They are produced using nanotechnology tools and techniques. According to some investigators, especially from Africa, Nigeria, where continuous electricity supply is a big challenge, the oxygen concentrators were fitted with solar panels for a continuous, uninterrupted supply of oxygen to the patient (18, 22).

We searched oxygen concentrators and portable oxygen concentrators on Science Direct for the time frame of 2017–2022, and the authors found a sharp increase in the number of articles in these 6 years. The key word used for this search was "oxygen concentrators." The number of articles drastically increased after the COVID-19 pandemic. Figure 1 shows the articles available in Science Direct within this time frame. So, from this research, we tried to bridge this gap with the latest information on oxygen concentrators which may help medical professionals in the future. It may also help in increasing the efficiency of president oxygen concentrators by using advancements in technology.

In the current review work, emphasis is given to the basic working principle of oxygen concentrators. Besides this, recent trends in the utilization of portable oxygen concentrators have been discussed. Nanosized zeolites are produced from the molecular zeolites using nanotechnology tools. These are crystalline microporous solids and have physicochemical properties similar to those of micron-sized crystals. The method for increasing the efficiency of current oxygen concentrators by using nanosized molecular zeolites is elegantly reviewed with an objective that the use of nanosized molecular zeolites may solve the demands of oxygen supply in a future pandemic or any disease outbreak.

2. Types of oxygen based on their applications

There are essentially two sorts of oxygen depending upon grade: medical and industrial. Many industries run their production facilities using commercial oxygen (23). Manufacturing oxygen for industrial

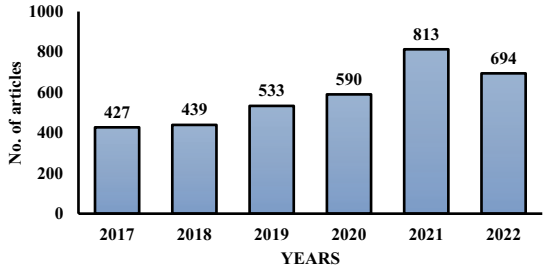


FIGURE 1
Year-wise articles published in the scientific domain on oxygen concentrators.

purposes is also required to meet industrial standards. Oxygen plants used in the generation of oxygen for industrial applications must meet the specifications of the industry. The procedure for generating medical and industrial oxygen is the same. Furthermore, medical oxygen is produced with a significant purity level, and the equipment used to produce it is made to the best of its ability (24). Medical oxygen is ultra-pure oxygen that has been created for use in the human body and is utilized in medical procedures. Medical oxygen is purified in the air separation process until it fulfills regulatory requirements (25).

In operating rooms, emergency departments, and ambulances, medical-grade oxygen is being used. Medical oxygen production requires adequate drug licenses and adherence to standard operating procedures, and it is recognized as a drug on the World Health Organization (WHO)'s list of essential medicines. To generate medical oxygen, it is also required to adhere to Indian Pharmacopeia (IP) guidelines (25). Figure 2 shows the types of oxygen as per the requirement and applications.

2.1. Liquid medical oxygen

Highly pure oxygen in the form of liquid medical oxygen (LMO) is being used for medical care and was invented for use in the human body (26). Liquification promotes smoother conveyance plus greater storage. These kinds of LMO can indeed be kept in a mobile cylinder that is attached to the main conduit. Due to the high concentration of liquid oxygen, a compact reservoir may hold much of the gas. Sarkar et al. in 2014 described the importance of liquid ventilation in treating several diseases and considered it effective over oxygen in the form of gas (4, 27).

3. Oxygen therapy

Oxygen therapy is the most commonly reliable method to treat hypoxemia in cardiovascular and respiratory system-related disorders (28, 29) and during pandemic disease outbreaks. All these patients require a continuous supply of medical-grade oxygen for the proper functioning of their vital organs and body. The method of distribution and equipment used for oxygen therapy influence the selection of variables, such as the patient's individual requirements and the discretion of the treating hospital personnel (30). Oxygen cylinders, oxygen production facilities, and oxygen concentrators are used to administer oxygen therapy.

3.1. Areas where oxygen therapy is required

Multiple chronic and acute medical disorders, including chronic asthma, cystic fibrosis, pulmonary hypertension, obstructive sleep apnea, heart failure, cases of anaphylaxis, severe trauma, seizure, or hypothermia, are managed by oxygen therapy (31–33). Whenever hypoxemia is found in any of the following situations, oxygen therapy is necessary for operating rooms as well. In the case of children and neonates, oxygen therapy is required during prematurity, birth asphyxia, acute sepsis, shock, severe pneumonia, meningitis, brain injury, coma, anemia, severe malaria, heart failure, acute asthma, etc. Among adults, oxygen therapy is required during, pneumonia, interstitial lung disease, pulmonary sarcoidosis, lower and upper respiratory infections, pneumoconiosis, severe malaria, meningitis, ischemia, etc. Figure 3 shows various conditions requiring oxygen in different age groups.

3.1.1. In adults

i. The main conditions requiring oxygen are hypoxemia, breathlessness, and dyspnea (34).
ii. Every patient's regular vitals must include pulse oximetry.
iii. Any patient with a SpO_2 below 90% on a pulse oximeter or clinical hypoxemia symptoms should be given oxygen, according to the recommendation (35).

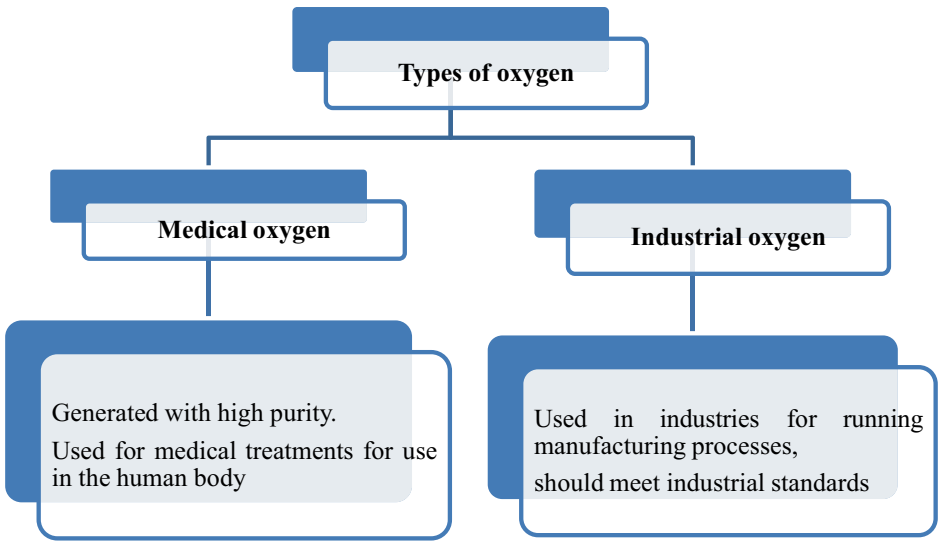


FIGURE 2
Medical oxygen versus industrial oxygen.

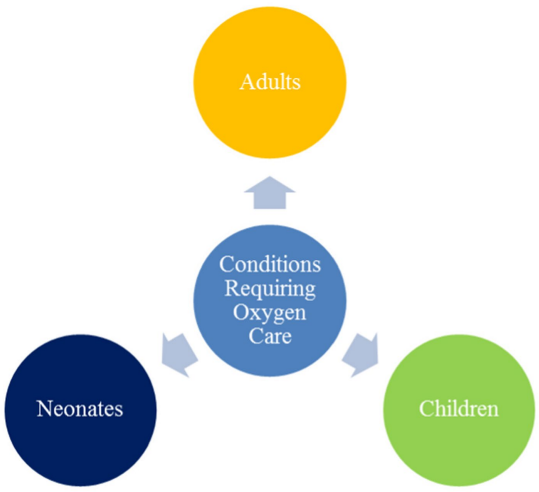


FIGURE 3
Conditions requiring oxygen care in clinical cases.

iv. Under some serious circumstances, such as brain injury/infection/coma, shock, sepsis, severe anemia, heart failure, or severe heart failure.
v. Whenever the Oxygen saturation, i.e., SpO_2 is <94%, oxygen should also be administered (26).
vi. While seeking medical examination as well as background, every seriously sick person should be given oxygen by paramedics, nurses, and other medical practitioners.

According to the clinical recommendations for oxygen therapy, oxygen should be administered to all patients who are in need.

3.1.2. Oxygen care in neonates

Newborn infants receiving oxygen therapy have lower normal oxygen saturation levels in their body as compared to the older neonates. And the condition of severity in low oxygen concentration in their body of neonates is high if they are delivered prematurely. Walsh et al. in 2009, reported to use oxygen for the treatment of several diseases like respiratory disorders and hypoxia, and the treatment process has positive and detrimental effects on the patients. The investigators reported that the extent of use of oxygen in neonates is not well known but they have shown that such treatment system has a positive role in the arsenal for neonates (36).

Dennery in 2010 reported that using medical oxygen in preterm infants is not recommended as it may have a detrimental effect in the long term in neonates. So, the liberal use of oxygen (blood oxygen saturation of >94%) and restrictive use (resulting in a blood oxygen saturation of <80–85%) are detrimental and may have a long-term negative effect. So, appropriate concentration and duration of oxygen may be effective in neonates and infants (37). Ramji et al. in 2015 reported that the use of oxygen had been challenged earlier in both clinical and biochemical results in neonates due to their adverse outcomes. But now, its use is recommended to treat ill neonates in the delivery room and neonatal intensive care unit (NICU). The use of oxygen has shown improvement in neonate survival (38).

3.1.3. Oxygen care in children's care

Among the most common respiratory ailments in children under the age of five is pneumonia, which accounts for over 15% of all annual fatalities worldwide. Out of this 15%, almost 13% of children with pneumonia develop hypoxemia (39–41). Pneumonia can be caused by bacteria, fungi and viruses (42). In such cases, the oxygen-holding capacity of alveoli and, ultimately, the lungs get reduced, and child needs urgent pure or medical oxygen. If pulse oximetry and oxygen therapy are consistently accessible, the annual child mortality rate could be reduced. Children living at or above 2,500 m above sea level with <90% blood oxygen levels as measured by pulse oximetry are required to receive oxygen therapy (43, 44). If normal oxygen saturation in children exposed to higher altitudes (>2,500 m above sea level) is lesser than that in children living at sea level, a SpO_2 level of 87 percent can be considered as a criterion for administering oxygen. Any children with a SpO_2 below 90% should indeed be administered oxygen while being evaluated by pulse oximetry (45).

4. Common oxygen supply system

There are several medical oxygen supply methods to patients, but the most common methods are the form of oxygen cylinders, oxygen concentrators, and liquid tanks & oxygen generators (46). The following methods are mainly used to administer medical oxygen (shown in Figure 4).

5. Requirements of medical gas (oxygen) and air points

All critical care areas of the hospitals, such as emergency wards, operation theatres (OT), intensive care unit (ICU), NICU, and labor room, should have an uninterrupted 24 × 7 h oxygen supply. Besides this high dependency unit (HDU) should also have a proper oxygen supply. As per industry norms, the requirement of oxygen supply in hospitals should be as shown in Table 1.

6. Side effects of breathing pure oxygen

Even though a low level of oxygen in the blood is not ideal, this does not entail that breathing extremely pure oxygen at high pressure and for long periods is beneficial to a patient's health. Breathing oxygen for a longer time and breathing oxygen at high pressure negatively impact an individual's health. Breathing pure oxygen for a longer time could lead to the following symptoms and diseases in the patient, shown in Figure 5. While, Figure 6 shows the side effects of breathing pure oxygen at high pressure.

7. Components of oxygen concentrators

The oxygen concentrators have several components like control, filters, air inlet, waste outlet, and flow splitter (47). The control

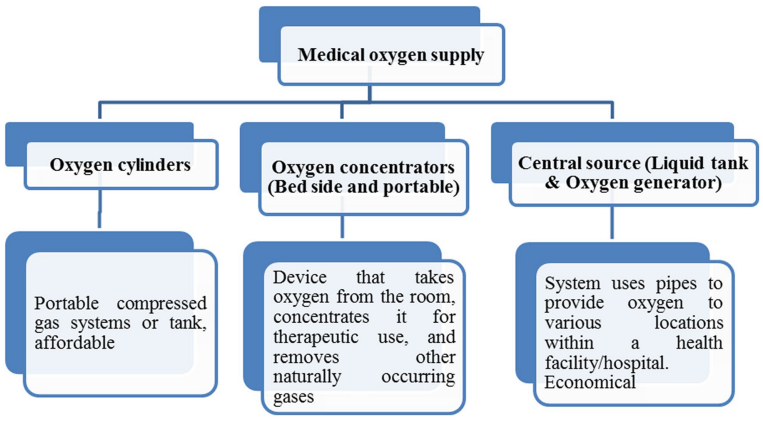


FIGURE 4
Medical oxygen supply systems.

TABLE 1 Requirements of oxygen supply in hospitals as per industry norms.

Specialties/ wards	Number of outlet points per bed		
Specialties/ wards	Number of outlets points		
	Oxygen	Suction	Air
Intensive care unit	2	2	1
Pediatric intensive care unit/neonatal intensive care unit	3	3	3
High dependency unit	2	2	1
Wards	1	1	1
Operation theater	2	2	1
Labor room	2	2	1
Cardiac intensive care units	2	2	1

ICU, intensive care units; PICU, pediatric intensive care unit; NICU, neonatal intensive care unit.

comprises the power switch, oxygen cock, and valve for adjustment below (48, 49). A series of filters are arranged in order, external coarse (gross particle filter), pre-filter, and inlet filter (compressor inlet filter (0.1 µm) in the oxygen concentrators. Besides this, it has a compressor (20 PSI), heat exchanger, 4-way solenoid-controlled valve, sieve canisters with zeolites, pressure equalization valve, check valve, pressure regulator, product canister, outlet filter (0.3 µm), and flow meter (50, 51). The zeolite crystals present in canisters have an average lifespan of 60,000 h (49). Figure 7 shows various components of an oxygen concentrator.

8. Principle of oxygen concentrators

Oxygen concentrators work on the principle of "*pressure swing adsorption*" (PSA) technology (52, 53). The word "*pressure swing adsorption*" implies that the applied pressure keeps on swinging, and consequently, there is continuous adsorption and desorption of gases, i.e., two stages from the molecular sieves. Two stages work in alternation, 1. Adsorption/Production 2. Blowdown/Purge (52). While Figure 8 shows detailed four phases of PSA technology of an oxygen concentrator. The compressed air (21% O_2+ 78% N_2) is supplied to one of the columns present in the canister. These columns are filled with adsorbent zeolite materials made of aluminum-silicate hydrates (54).

Firstly, column one gets compressed air, during which N_2 gets adsorbed on the zeolites' surface while the O_2 (present in lower content in air) is passed through these zeolite columns and is collected in an oxygen tank. Due to the continuous adsorption first column gets saturated, so the valve closes, and pressurized air is moved into the second canister containing molecular sieves (55). During this period, the pressure on the earlier column gets lowered, due to which the adsorbed nitrogen gas is released into the surrounding. This particular step, where the column releases the N_2 from the column and gets prepared for the next cycle, is called regeneration (56). Again, in the next cycle, another column will be regenerated by releasing the adsorbed N_2, this adsorption and desorption continue due to a swing in pressure; hence it is called "*pressure swing technology*."

9. Working of oxygen concentrators

A stable supply of oxygen-enriched airflow is delivered by oxygen concentrators. Devices called oxygen concentrators (also known as oxygen generators) drive indoor air through several filters to eliminate particles, germs, and other impurities (57). The first stage in the concentration procedure includes pumping air into one of the two cylinders, which comprise a semi-permeable membrane or a "molecular sieve" element. Next, nitrogen is removed, generating pure oxygen (90 percent or more) and a minor amount of certain other gases present in indoor air (58–61). An accessible source of oxygen-enriched air is an oxygen concentrator. Nitrogen is desorbed and pulled outside into the environment simultaneously in another tank. The second step includes the cylinders' functionality being reverted in a scheduled loop to ensure that patients receive a steady oxygen supply. Certain kinds of high-flow

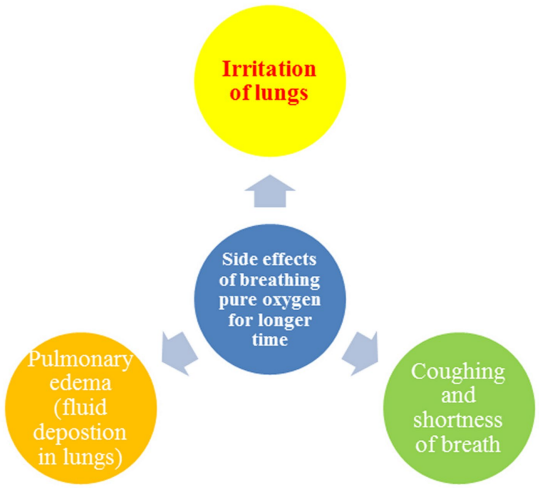


FIGURE 5
Side effects of breathing pure oxygen.

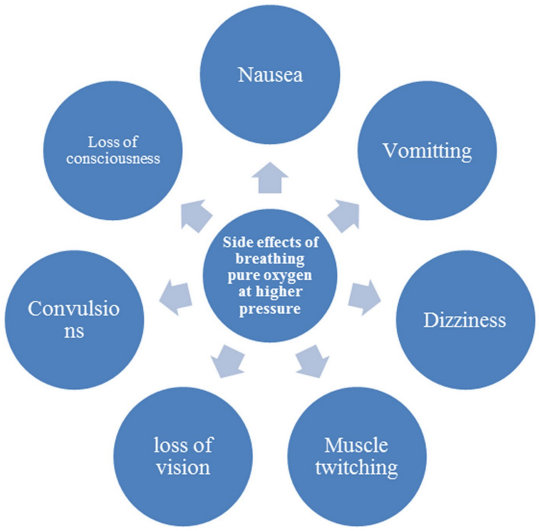


FIGURE 6
Side effects of breathing pure oxygen at high pressure.

oxygen concentrators can produce up to 10 L/min of oxygen, whereas low-flow oxygen concentrators typically give an oxygen flow of 0.5–5 L/min (62, 63).

In essence, continuous flow dose administration and pulse mode distribution are indeed the two different ways oxygen is administered in oxygen concentrators. While pulse mode delivery pulses an oxygen "bolus" (57) whenever the user starts to breathe, continuous flow dose treatment provides a consistent, smooth, and efficient oxygen flow depending on the configuration value of $Lmin^{-1}$.

Since it provides oxygen through the cannula whenever you breathe, the pulse dose setting is typically utilized during the day. Additionally, pulse dosage concentrators have a much more compact design as well as a better battery life (63). The working principle of an oxygen concentrator is shown below in Figure 9.

10. Types of oxygen concentrators

Both stationary and portable oxygen concentrators are available. A continuous oxygen supply is provided by stationary (home) concentrators, which have an average weight of around 10 kg and a flow rate of 0.5 to 10–15 L/min. For long-term oxygen therapy (LTOT) users who want a smaller, portable oxygen supply in a movable apparatus, portable oxygen concentrators are indeed the latest innovation available (64, 65). Weight, size, oxygen flow settings, range of L/min, battery life, and other characteristics of portable concentrators differ (63). Table 2 shows the major differences between a portable oxygen concentrator (POC) and a stationary oxygen concentrator (SOC).

A more recent choice is a super-compact home concentrator, which might weigh as little as 4.5 kg. These portable devices operate on both alternating current (AC; for example, from a wall outlet) and direct current (DC; for example, from a cigarette lighter socket; e.g., they can be smoothly shifted from one place to the other or they can be transported by car during travel). Presently, these can handle oxygen flow rates of up to 2 L/min (63). Zeolites are used in various processes to improve product quality, processing rates, energy efficiency, and the environmental consequences of the oxygen purification process (66). Figure 10A is a stationary oxygen concentrator, while 10B is a POC.

11. Clinical applications of oxygen concentrators

In the medical profession, there have been four main instances under which oxygen concentrators are being used: oxygen therapy in small hospitals; oxygen therapy for pre-term neonates with chronic lung disease who need oxygen after discharge; oxygen therapy for older children with chronic obstructive pulmonary disease, pneumonia, pulmonary embolism, or emphysema; and oxygen therapy for children with acute respiratory distress syndrome (ARDS) with extensive fibrosis who need O_2 therapy for a prolonged period. Besides this, oxygen concentrators could be used in hospitals during surgery to maintain tissue oxygenation during anesthesia and the resuscitation of patients (67). Figure 11 shows the clinical applications of oxygen concentrators.

12. Supportive data regarding utilization of oxygen concentrators

Ress and Dudley (1998) (68) reported the role of oxygen therapy, especially oxygen or oxygen concentrators for patients being treated at home. Employing a recently designed polymer of poly [1-(trimethylsilyl)-1-propyne] with an oxygen permeability of $61 \times 10\ cm^3$ (STP) $cm/cm^2\ s\ cmHg$, which itself is 17 times greater than those of the membrane material of traditional concentrators, Akutsu et al. in 1990 built a small, light-weight oxygen concentrator. The oxygen and nitrogen selectivity was 1.80. The dimension and weight of the O_2 concentrator were about $325 \times 180 \times 150$ mm 4.0 kg, respectively. It generated an oxygen concentration of about 30%, and the maximum flow rate was 41/min (68). Ritz et al. (69) suggested using oxygen concentrators during mass causality situations. A range

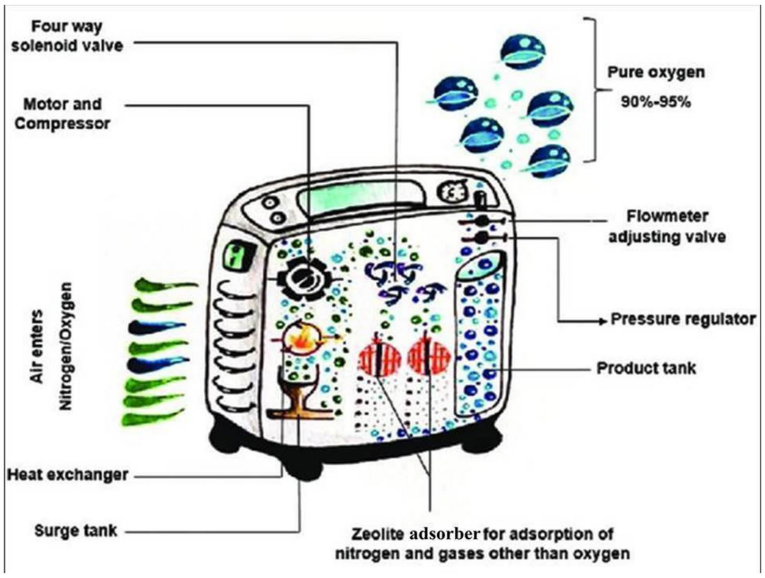


FIGURE 7
Various components of an oxygen concentrator [adopted from Todur et al. (47)].

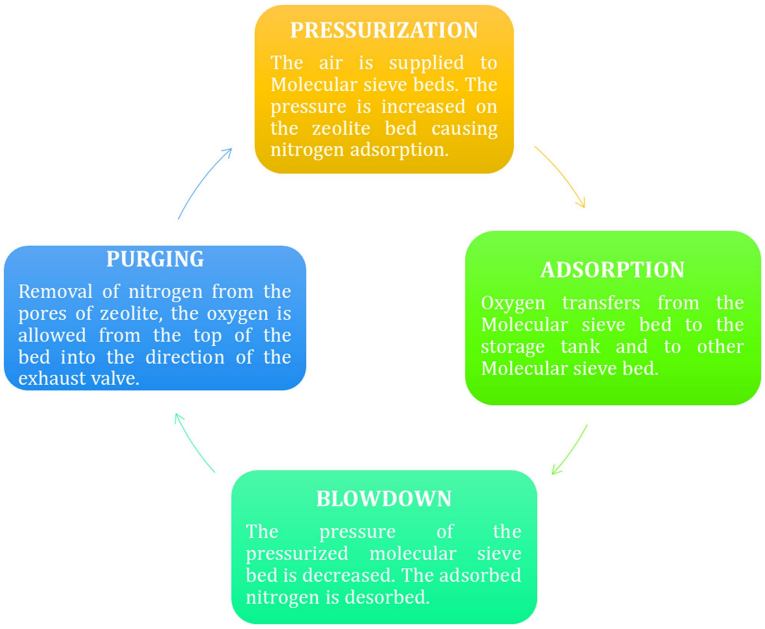


FIGURE 8
Four stages of PSA cycle (51).

of oxygen concentrator layouts is accessible, including smaller, more portable units that may serve a single patient and bigger units that could also serve a group of patients or an entire facility (69).

Pollock and Natoli (70) reported the use of chemical oxygen generation for oxygen therapy. To assess the effectiveness of the emOx mobile non-pressurized emergency powdered oxygenation delivery system. This product, which chemically creates oxygen, is promoted to be used as urgent first aid until trained medical support is accessible (70). According to McCoy et al. (71), there are now more possibilities for home oxygen therapy equipment than there were a few years ago due to technological advancements, financial aid from third-party providers, and patient demands. With the development of intermittent-flow delivery, oxygen concentrators that yield 99 percent oxygen authenticity have replaced packaged gas systems (oxygen concentrators) that delivered oxygen that was 99 percent pure, according to the United States Pharmacopeia (71, 72).

In patients with chronic obstructive pulmonary disease (COPD), Yanez et al. (73) documented oxygenation using a single portable

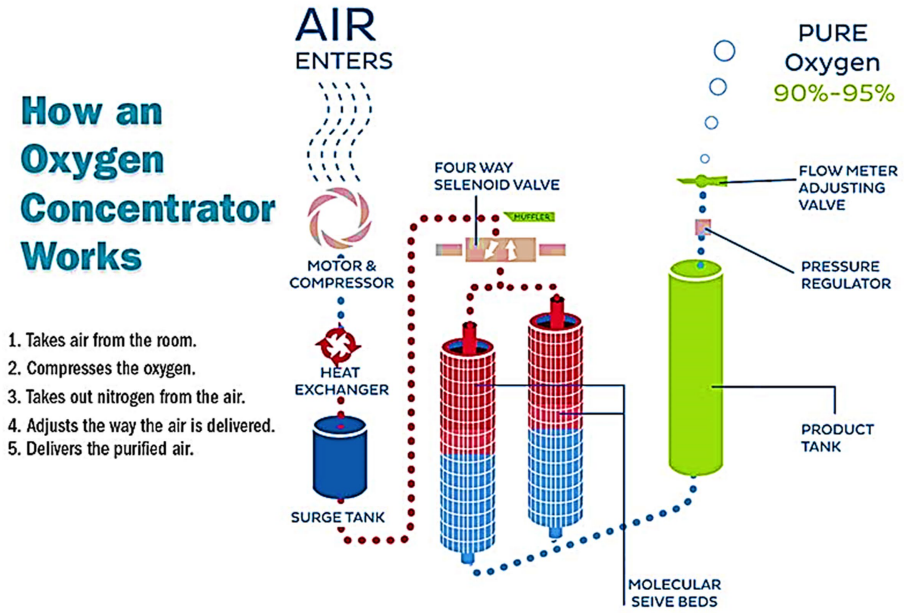


FIGURE 9
Working of an oxygen concentrator.

TABLE 2 Major differences between portable and stationary oxygen concentrators.

Portable oxygen concentrator	Stationary oxygen concentrator
Small, lightweight	Large in size, heavy in weight (mean wt ~ 10 kg)
Greater flexibility with power sources	Lesser flexibility with power sources
Lower oxygen output and high cost	higher oxygen output and lower costs

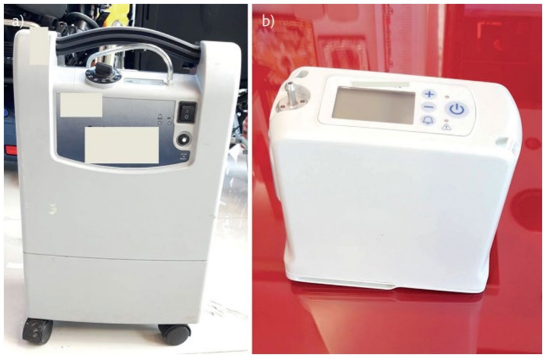


FIGURE 10
Oxygen concentrators. **(A)** Stationary oxygen concentrator. **(B)** Portable oxygen concentrator adapted from Hardvella (63).

pulse-dose oxygen-conserving device and integrated stationery and portable oxygen delivery systems. They said that portable oxygen devices, i.e., oxygen concentrators, simplify and facilitate patient therapy. The subjects chose to use a single portable oxygenation system when in an ambulance or at home. Moreover, fixed and portable systems functioning together generated higher amounts of oxygen than portable systems working alone (73). Katz et al. (74) analyzed the oxygen uptake during rest and exercise in mild COPD patients using portable oxygen concentrators in order to improve the effectiveness of oxygen generation and nitrogen adsorption in oxygen concentrators (74).

Pan et al. (75) suggested the usage of nanosized zeolites. They suggested the device as a basic requirement for lung infection-associated patients. To effectively adsorb nitrogen from the air, a 13X nanosize zeolite with Li^+ exchanged is utilized as the adsorbent. To better understand the pressurization and depressurization processes taking place inside the microporous region of nanosized zeolites, a dynamic model of the pressure and vacuum swing adsorption units was created (21). The effectiveness of continuous versus pulsed oxygen administration was compared by Chen et al. in 2017 utilizing an accurate adult nasal airway replica. The main objectives of this work were to examine steady flow (SF) from a compressed oxygen tank to PF for a commercial POC and to construct a prospective *in vitro* analysis for inhaling oxygen supply employing a set of plausible airways replicas (75).

In a pediatric ward in Malawi, Meyers et al. in 2018 documented employing bubble continuous positive airway pressure (bCPAP) to treat seriously unwell children. Humidified bCPAP air/oxygen flow was given by customized oxygen concentrators or oxygen cylinders. Further research is required to determine the function of bCPAP and other non-invasive ventilator support methods in an effective healthcare program for seriously sick children with MOF at the tertiary and district hospital levels in low-resource economies (76). Branson in 2018 stated that patients with COPD and severe resting hypoxemia were shown to have a greater chance of survival when receiving long-term oxygen treatment (LTOT) at residence. It has already been demonstrated that oxygen supplementation administered by an oxygen concentrator during physical activity and exercise

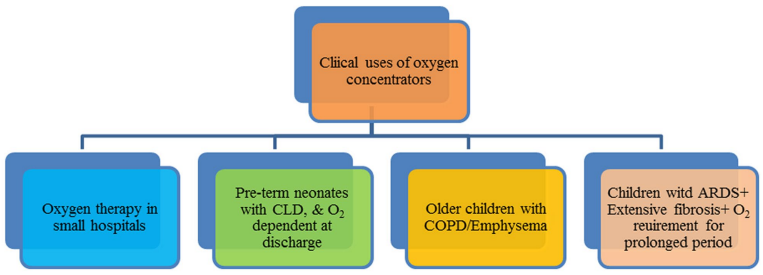


FIGURE 11
Clinical applications of oxygen concentrators.

reduces symptoms and maintains arterial oxygen saturation, but it does not enhance long-term effectiveness (77). Melani et al. (78) reported the importance of oxygen-producing devices (O_2 concentrators) in home oxygen therapy. Besides this, they also explained the role of a pulse oximeter, etc., in-home oxygen therapy (78).

Pulsed oxygen delivery through portable oxygen concentrators against continuous flow oxygen delivery was compared in an *in-vitro-in silico* research by Chen et al. in 2019. The effectiveness of four POCs with continuous flow oxygen was compared using *in vitro* bench measurements and *in silico* numerical simulations by anticipating the FIO2 at the trachea and entering the acini. In respect of volume-averaged FIO2, continuous flow oxygen provided adequate (>2% absolute) oxygen for all nominally equivalent pulse flow levels of >2 (79). Bench-wise comparative research between modern portable oxygen concentrators and various breathing techniques was conducted by Martin et al. in 2019. Considering three realistic breathing patterns, resting, and oronasal inhalation while sleeping, three modern devices were bench-tested (80). In Madrid, Spain, patients undergoing portable oxygen therapy were the subject of a telephone-based study conducted by Alises et al. in 2019. The survey looked at patients' present situations, behaviors, and perceptions.

Patients selected from a registry undergoing treatment with portable oxygen were interviewed over the phone. Most patients used mobile oxygen concentrators (99.59 percent) (81). According to Litch and Bishop (82), using oxygen concentrators to give medical oxygen in isolated, high-altitude environments significantly impacts supply and related costs. In a rural hospital located at 3,900 m in the Nepal Himalayas, researchers highlighted the significance of oxygen concentrators. The investigators also stated that oxygen concentrations of more than 80% might be sustained at delivery flow rates of 2–5 L per minute (82). According to the findings of the research conducted by Sardesai et al. (83), portable oxygen concentrators are recommended to be utilized for home-isolated COVID patients. This is particularly the case for patients who do not exhibit severe symptoms and for whom there is no requirement for BIPAP. Through the follow-up with COVID-19 patients undergoing home oxygen therapy, feedback was obtained (83).

According to Shen in 2020, oxygen therapy has the potential to improve the antiviral response of the immune system. Treatment with nighttime oxygen may stop the progression of COVID-19. SARS-CoV2 is known to use ACE2, which is the same cell invasion receptor as SARS-CoV2. It is secure and simple to apply in therapeutic settings (a home O_2 concentrator is enough for a patient) (84). According to Duke et al. in 2020, oxygen therapy is a crucial medical treatment and a critical part of functional hospital setups. They emphasized the application of oxygen concentrators in especially low-income countries, where medical facilities are not so well developed. So, it is best suited for African and Asia Pacific countries, which lack better medical infrastructure (85).

Cuerpo et al. (86) suggested the use of oxygen concentrators along with the noninvasive ventilation device in interstitial lung disease patients, which can improve home oxygen therapy. They employed both oxygen concentrators alone and in combination with non-invasive ventilation, and they discovered that the average SaO_2 increased to 91% (88–93) versus 88% (86–90%); $p = 0.0005$ as well as a decline in the measure of time with oxygen saturation below 90%: 36% (6–56%) versus 58% (36–77%); p 0.0001 (86). In Sabah, Malaysia, during the COVID-19 pandemic, Cheah et al. (87), recommended using a dual oxygen concentrator system for manual breathing. According to the investigators, oxygen concentrators are a life-saving alternative for patients, and they could even save a severely ill patient during COVID (87). For use in medical applications, Vemula and Matthew in 2021 designed an experimental "Snap-on" and an independent single-bed oxygen concentrator. For continuous oxygen supply, a unique single-bed, "Snap-on," and independent medical oxygen concentrator design based on a rapid pressure swing adsorption technique was explored. When connected to a preexisting compressed gas stream, the Snap-on concentrator's configuration makes it simple to use the devices and efficiently produce oxygen for medical uses. Because of its separate compressor and ease of portability, the Snap-on concentrator is extremely significant for oxygen therapy, meeting the demands of a higher number of patients in the circumstances like COVID-19 (56).

In 38 remote health institutions in nine regions of Papua New Guinea, Pulsan et al. (88) examined a scheme for enhancing credible oxygen therapy using oxygen concentrators, pulse oximeters, and renewable solar power. In rural and remote hospitals and healthcare institutions, solar-powered oxygen systems can be installed on a broad scale and have been linked to a decrease in child fatalities and a reduction in referrals (88). According to Madaan et al. (89), rural India's oxygen needs should focus on employing a supply of substantially pure oxygen that is secure, affordable, simple to access, and mass-producible. The arrangement of a self-sustaining oxygen concentrator (pressure swing adsorption with multiple molecular sieve technology) that provide oxygen at high flow rates through a centrally controlled distribution network to 100 or even more bedded community hospitals, with backup from an oxygen bank

of 10 × 10 cylinders, may be able to achieve this. It could also act as a facility for replenishing local oxygen cylinders for medical emergencies inside the hospital premises and for delivery to ambulances, primary health centers, and other remote locations (89).

13. Types of zeolites used in oxygen concentrator

Zeolites are micron-sized, crystalline, porous compounds made up of alumina and silica hydrates along with an alkali metal (90). Its structure has numerous pores, making it suitable as an adsorbent. It is widely used in the oxygen concentrator due to its ability to withstand higher temperatures and its tendency to regenerate completely aster adsorption (51). Zeolite molecular sieves for oxygen concentrators come in two primary varieties: sodium type and lithium type (91). The oxygen concentrator is compact and easy to transport because lithium-type zeolite molecular sieves are much more effective than sodium-type zeolite molecular sieves that decreases the amounts of oxygen generation. Since sodium oxygen molecular sieve is considerably less expensive than lithium molecular sieve, sodium oxygen molecular sieve is also readily available in markets.

All the above factors make oxygen concentrators more economical and environmentally friendly (51). Recently Sami et al. (51) studied various types of zeolites used in oxygen concentrators and concluded that there are mainly four types of zeolites used as adsorbents. These four types of zeolites are 5A zeolite, Oxysiv 5, 7 & Sylobead MS S 624, LiX zeolite, and LiLSX zeolite. As per their investigation, it was concluded that various absorbents in oxygen concentrators have different cycles and purity of oxygen produced by them (51). The properties of these four commonly used zeolites are summarized in Table 3.

14. Drawbacks of micron-sized molecular sieves

Since the size of the currently used molecular sieves is in microns, less nitrogen could be adsorbed on their surface due to size. Consequently, the efficiency of oxygen generation, as well as the purity of oxygen, are both less. So, to overcome this, ultrafine zeolites have to be used to enhance the efficiency and purity of the oxygen. Zeolites are widely used in oxygen concentrators to adsorb the nitrogen on their surface. This process takes place under pressure swing adsorption technology, which concentrates oxygen from the air. The zeolites have more affinity for nitrogen and less affinity for oxygen. Since most oxygen concentrators use micron-sized molecular sieves to adsorb the nitrogen, their efficiency is not 100%; rather, it falls to 87–93%, depending on several other factors (92).

15. Role of nanotechnology in oxygen concentrators

There are several procedures by which the efficiency of such oxygen concentrators and the purity of oxygen can be achieved. One such process is the application of nanozeolites, which are used for this purpose since they are smaller in size and contain more reactive sites on their surface (93). Nanozeolites are a type of zeolites which are produced from the molecular zeolites and these have particle distribution and sizes of <200 nm. Due to their small size, these nanozeolites exhibit significant surface–to–volume ratios (SVR) and large surface values. More nitrogen will be adsorbed on the surface of nanozeolites compared to micron-sized zeolites because of the high surface area-to-volume ratio (94–96).

Some investigators have used nanozeolites in oxygen concentrators for nitrogen adsorption and obtained satisfactory results. Some of the examples are provided below in chronological order. In a continuous adsorption and desorption cycle with a cycle period of 90 s, Pan et al. (92), employed nanozeolites as molecular sieves in which the outcome of the oxygen concentrator is a flow of enriched oxygen at about 90 vol percent. The adsorption column measures 20 cm in length and 3 cm in diameter. To effectively adsorb nitrogen from the air, a 13X nanosize zeolite with Li^+ exchanged is utilized as the adsorbent. To better understand the pressurization and depressurization processes taking place inside the microporous region of nanosized zeolites, a simulation of the pressure and vacuum swing adsorption units was devised (92). Besides this, several investigators have also reported the surface modification of such nanozeolites by other metallic particles to make the process more efficient (1, 97–99).

In this regard, chabazite (CHA) zeolites were manufactured at different range diameters of 120–300 nm, whereas the smaller sample (120 nm) also consisted of tiny particles (around 20 nm) (100). These small units of the CHA zeolites are basically used along with zeolites for gas separation technologies. The design and development of such nano-sized zeolite-based specimens are highly appreciated for constructing vacuum swing adsorption devices due to their thermal stability and compressive stress. Moreover, the hybrid CHA zeolites are prepared by doping a few desired ions, such as Sr^{2+}, K^+, and Na^+ cations, by avoiding organic substances (100). The as-prepared membranes are useful to form a chemically stable system as the cation species interact well with the negatively occurring aluminum oxygen sites $(AlO_2)^-$ in a tetrahedral geometry (101). Nowadays, various models have been explored to design and develop zeolite-based

TABLE 3 Literature survey on zeolites used for oxygen concentrators adopted from Pan et al. in 2017 and Semi et al. in 2022 (92).

Absorbent	Cycle type	Cycle duration(s)	Operating pressure (bar)	Purity (%)	Flow rate
5A zeolite	PSA 2-step	100	Ph = 1.52, P1 = 1.01	85	–
Oxysiv 5,7 & Sylobead MS 624	PSA 2-step	18	Ph = 3, P1 = 1.945	94.5	3.7
LiLSX zeolite	PSA 2-step	3–9	Ph = 4, P1 = 1	90	1–3
Lix zeolite	PSA 2-step	3–5	Ph = 3.04–4.05, P1 = 1.01	90	5

oxygen concentrators. For example, a molecular sieve with particular model numbers and activated alumina in PSA oxygen generators.

The higher production of O_2 includes a larger amount of nitrogen adsorption. Additionally, the selectivity in N_2 and O_2 (nitrogen/oxygen) allows it to be called with different model names, such as the JLOX-500 series molecular sieve. Using nanotechnologies, these systems show better wear resistance and good service rate as the pore sizes, surface, and structural modifications are carried out under preparation procedures (102). The use of nano-based techniques felicitates a cost-effective oxygen production with lower energy consumption by using the nano-sized zeolites and their derivatives using metal cations and organic units. Thus, the chemical structure of the zeolite is extensively recommended for the efficient oxygen concentrator due to its chemical and physical strength, including its $(SiO_4)^{4+}$ and $(AlO_4)^{5+}$ tetrahedral geometry sharing the partially negatively charged oxygen atoms. Extensively, the isotherm concept has been derived from understanding the isotherm adsorption of the zeolites using Langmuir, Freundlich, and Tempkin model's theorem, and the characteristics of adsorption application are being studied (103).

Pseudo-first order, pseudo-second order, Bangham, intra-particle diffusion, and Elovich models were used to assess the kinetics of the adsorption objects, demonstrating the feasibility of the applicability of gaseous adsorption (103). As oxygen concentrators basically include gas compressors and adsorption sciences, nano-sized zeolites have been encouraged in this sector. Overall, stronger structural aspects with the change in cationic oxidation states help to modify the framework of the zeolite, which affects the adsorption nature and separates the gases, mainly O_2 and N_2/O_2. These physicochemical properties of the synthetic zeolite with their morphological changes could be widely used in modern nanotechnology and sciences toward newly designed oxygen concentrators/systems and their accessories (104–106). Overal evolution in use of molecular zeolites to nano-zeolites has gained importance to tackle the O_2 supply chain issue that had been severely felt in medical care during the pandemics in developing countries such as India and similar countries (107–110).

16. Conclusion

Oxygen is one of the basic and essential medical drugs required by patients in less to highly severe cases. The demand and supply of mobile oxygen generators have increased drastically in the last couple of years. So, portable oxygen concentrators, initially proven life-supportive in hilly areas in African countries, have now gained importance. Its economical, mobile natures, and ease of handling, have made basic needs in every house. The utilization of four basic types of zeolites as an adsorbent has limitations in the sense of generation, purity of oxygen, etc., and efficiency being micron in size. So, the nanosized zeolites can potentially make the process of adsorption and desorption in oxygen concentrators more effective due to their small size and high surface area-to-volume ratio. Nanosized zeolites have the potential to be a game-changer in the delivery of pure oxygen to the patient in the face of current and future pandemics caused by a wide range of viruses and bacteria.

Author contributions

VY, BP, and DKS: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, roles and writing – original draft, and writing – review and editing. NC, GI, AR, BiS, and BhS: concept, writing – original draft, writing – review and editing, and revision. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors are thankful for proving basic infrastructure facilities by Mody University of Science and Technology, Sikar, Rajasthan, India.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Williams E, Piaggio D, Andellini M, Pecchia L. 3D-printed activated charcoal inlet filters for oxygen concentrators: a circular economy approach. *Dev Eng*. (2022) 7:100094. doi: 10.1016/j.deveng.2022.100094

2. Urich MD, Vemula RR, Kothare MV. Implementation of an embedded model predictive controller for a novel medical oxygen concentrator. *Comput Chem Eng*. (2022) 160:107706. doi: 10.1016/j.compchemeng.2022.107706

3. Dhont J, di Tella M, Dubois L, Aznar M, Petit S, Spałek M, et al. Conducting research in radiation oncology remotely during the COVID-19 pandemic: coping with isolation. *Clin Transl Radiat Oncol*. (2020) 24:53–9. doi: 10.1016/j.ctro.2020.06.006

4. Sarkar M, Niranjan N, Banyal PK. Mechanisms of hypoxemia. *Lung India*. (2017) 34:47. doi: 10.4103/0970-2113.197116

5. Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its clinical predictors. *Indian J Pediatr*. (2006) 73:777–81. doi: 10.1007/BF02790384

6. Chen YL, Chen YC, Wang HT, Chang YT, Fang YN, Hsueh S, et al. The impact of intermittent hypoxemia on left atrial remodeling in patients with obstructive sleep apnea syndrome. *Life*. (2022) 12:12. doi: 10.3390/life12020148

7. Hirota K, Mayahara T, Fujii Y, Nishi K. Asymptomatic hypoxemia as a characteristic symptom of coronavirus disease: a narrative review of its pathophysiology. *COVID*. (2022) 2:47–61. doi: 10.3390/covid2010004

8. Chiumello D, Brioni M. Severe hypoxemia: which strategy to choose. *Crit Care*. (2016) 20:132. doi: 10.1186/s13054-016-1304-7

9. Cheng S, Luo Y, Zhang J, Shi R, Wei S, Dong K, et al. The highly effective therapy of ovarian cancer by bismuth-doped oxygen-deficient BaTiO3 with enhanced sono-piezocatalytic effects. *Chem Eng J*. (2022) 442:136380. doi: 10.1016/j.cej.2022.136380

10. Nakamura M, Noguchi K. Tolerant mechanisms to O2 deficiency under submergence conditions in plants. *J Plant Res*. (2020) 133:343–71. doi: 10.1007/s10265-020-01176-1

11. Tiep B, Carter R, Zachariah F, Williams AC, Horak D, Barnett M, et al. Oxygen for end-of-life lung cancer care: managing dyspnea and hypoxemia. *Expert Rev Respir Med*. (2013) 7:479–90. doi: 10.1586/17476348.2013.816565

12. Gardner B. The manufacture, storage and supply of medical gases. *S Afr Fam Pract*. (2013) 55:S40–3. doi: 10.1080/20786204.2013.10874363

13. Chen Y, Wang Q, Lei J, Liu Q, He W, Liu S, et al. Design and engineering application of medical oxygen supply system in novel coronavirus pneumonia treatment hospital. *J Build Eng*. (2021) 44:103170. doi: 10.1016/j.jobe.2021.103170

14. Wood MH, Hailwood M, Koutelos K. Reducing the risk of oxygen-related fires and explosions in hospitals treating Covid-19 patients. *Process Saf Environ Prot*. (2021) 153:278–88. doi: 10.1016/j.psep.2021.06.023

15. Singh S, Sharma BB. Severe acute respiratory syndrome-coronavirus 2 and novel coronavirus disease 2019: an extraordinary pandemic. *Lung India*. (2020) 37:268–71. doi: 10.4103/lungindia.lungindia_170_20

16. Hardavella G, Karampinis I, Frille A, Sreter K, Rousalova I. Oxygen devices and delivery systems, Oxygen devices and delivery systems. *Breathe*. (2019) 15:e108–16. doi: 10.1183/20734735.0204-2019

17. Dobson MB. Oxygen concentrators and cylinders. *Int J Tuberc Lung Dis*. (2001) 5:520–3.

18. Bakare AA, Graham H, Ayede AI, Peel D, Olatinwo O, Oyewole OB, et al. Providing oxygen to children and newborns: a multi-faceted technical and clinical assessment of oxygen access and oxygen use in secondary-level hospitals in Southwest Nigeria. *Int Health*. (2019) 12:60–8. doi: 10.1093/inthealth/ihz009

19. Shiao SY, Ou CN. Validation of oxygen saturation monitoring in neonates. *Am J Crit Care*. (2007) 16:168–78.

20. Myers S, Dinga P, Anderson M, Schubert C, Mlotha R, Phiri A, et al. Use of bubble continuous positive airway pressure (bCPAP) in the management of critically ill children in a Malawian paediatric unit: an observational study. *BMJ Open Respir Res*. (2019) 6:e000280. doi: 10.1136/bmjresp-2018-000280

21. Pan M, Omar HM, Rohani S. Application of nanosize zeolite molecular sieves for medical oxygen concentration. *Nano*. (2017) 7:7. doi: 10.3390/nano7080195

22. Duke T, Pulsan F, Panauwe D, Hwaihwanje I, Sa'avu M, Kaupa M, et al. Solar-powered oxygen, quality improvement and child pneumonia deaths: a large-scale effectiveness study. *Arch Dis Child*. (2021) 106:224–30. doi: 10.1136/archdischild-2020-320107

23. Singh A, Shivapuji A. *S3 medical oxygen generator design document for 3 Nm3/h medical oxygen generation system medical grade oxygen generation view project DSTRHEES view project*. (India: Indian Institute of Science) (2021). doi: 10.13140/RG.2.2.10172.56969

24. Priority medical devices list for the COVID-19 response and associated technical specifications. (2020).

25. Ackley MW. Medical oxygen concentrators: a review of progress in air separation technology. *Adsorption*. (2019) 25:1437–74. doi: 10.1007/s10450-019-00155-w

26. PIB Mumbai. *Liquid Medical Oxygen: Explainer*. Ministry of Health and Family Welfare (2021). Available at: https://pib.gov.in/PressReleasePage.aspx?PRID=1716197 [Accessed on April 14, 2023]

27. Sarkar S, Paswan A, Prakas S. Liquid ventilation. *Anesth Essays Res*. (2014) 8:277–82. doi: 10.4103/0259-1162.143109

28. Martin DS, Grocott MPW. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia*. *Crit Care Med*. (2013) 41:423–32. doi: 10.1097/CCM.0b013e31826a44f6

29. Okba NMA, Müller M, Li W, Wang C, GeurtsvanKessel C, Corman V, et al. Severe acute respiratory syndrome coronavirus 2−specific antibody responses in coronavirus disease patients. *Emerg Infect Dis J*. (2020) 26:1478–88. doi: 10.3201/eid2607.200841

30. Fairley HB. Oxygen therapy for surgical patients. *Am Rev Respir Dis*. (1980) 122:37–44. doi: 10.1164/arrd.1980.122.5P2.37

31. Reiter J, Gileles-Hillel A, Cohen-Cymberknoh M, Rosen D, Kerem E, Gozal D, et al. Sleep disorders in cystic fibrosis: a systematic review and meta-analysis. *Sleep Med Rev*. (2020) 51:101279. doi: 10.1016/j.smrv.2020.101279

32. Jiang B, Wei H. Oxygen therapy strategies and techniques to treat hypoxia in COVID-19 patients. *Eur Rev Med Pharmacol Sci*. (2020) 24:10239–10246. doi: 10.26355/eurrev_202010_23248

33. Allardet-Servent J, Sicard G, Metz V, Chiche L. Benefits and risks of oxygen therapy during acute medical illness: just a matter of dose! *Rev Med Interne*. (2019) 40:670–6. doi: 10.1016/j.revmed.2019.04.003

34. Baldwin J, Cox J. Treating dyspnea: is oxygen therapy the best option for all patients? *Med Clin N Am*. (2016) 100:1123–30. doi: 10.1016/j.mcna.2016.04.018

35. Rebecca M. Pulse oximetry: what the nurse needs to know. *Nurs Stand*. (2017) 31:42–5. doi: 10.7748/ns.2017.e9940

36. Walsh BK, Brooks TM, Grenier BM. Oxygen therapy in the neonatal care environment. *Respir Care*. (2009) 54:1193–202.

37. Dennery PA. Oxygen administration in the care of neonates: a double-edged sword. *Chin Med J*. (2010) 123:2938–42. doi: 10.3760/cma.j.issn.0366-6999.2010.20.034

38. Ramji S, Saugstad OD, Jain A. Current concepts of oxygen therapy in neonates. *Indian J Pediatr*. (2015) 82:46–52. doi: 10.1007/s12098-014-1571-8

39. Karki S, Fitzpatrick AL, Shrestha S. Risk factors for pneumonia in children under 5 years in a teaching Hospital in Nepal. *Kathmandu Univ Med J*. (2015) 12:247–52. doi: 10.3126/kumj.v12i4.13729

40. Das CS. Acute respiratory ailments in pediatric age group and role of CRP in diagnosis and management In: W Ansar and S Ghosh, editors. *Clinical significance of C-reactive protein*. Singapore: Springer Singapore (2020). 213–48.

41. Keith Grimwood ABC. Long term effects of pneumonia in young children. *Pneumonia*. (2015) 6:101–14. doi: 10.15172/pneu.2015.6/621

42. Shan C, Yao YF, Yang X, Zhou YW, Gao G, Peng Y, et al. Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in rhesus macaques. *Cell Res*. (2020) 30:670–7. doi: 10.1038/s41422-020-0364-z

43. Dimich I, Singh PP, Adell A, Hendler M, Sonnenklar N, Jhaveri M Evaluation of oxygen saturation monitoring by pulse oximetry in neonates in the delivery system. *Can J Anaesth*. (1991) 38:985–8. doi: 10.1007/BF03008616

44. Rauniyar NK, Pujari S, Shrestha P. Study of oxygen saturation by pulse oximetry and arterial blood gas in ICU patients: a descriptive cross-sectional study. *J Nepal Med Assoc*. (2020) 58:789–93. doi: 10.31729/jnma.5536

45. Ross PA, Newth CJL, Khemani RG. Accuracy of pulse Oximetry in children. *Pediatrics*. (2014) 133:22–9. doi: 10.1542/peds.2013-1760

46. Little CM, Merritt M, Wentworth A. An improvised oxygen supply system for pandemic and disaster use. *Acad Emerg Med*. (2009) 16:558–63. doi: 10.1111/j.1553-2712.2009.00400.x

47. Todur P, Chaudhuri S, Eeshwar M, Teckchandani D, Venkateswaran R. Oxygen sources and delivery devices: essentials during COVID-19. *Indian J Respir Care*. (2021) 10:171. doi: 10.4103/ijrc.ijrc_63_21

48. Celli BR, Zuwallack RL. 105 – pulmonary rehabilitation In: VC Broaddus, RJ Mason, JD Ernst, TE King, SC Lazarus and JF Murrayet al, editors. *Murray and Nadel's textbook of respiratory medicine*. *6th* ed. Philadelphia: W.B. Saunders (2016). 1821–1831.e3.

49. Flecknell P. Chapter 1 – basic principles of Anaesthesia In: P Flecknell, editor. *Laboratory animal Anaesthesia*. *4th* ed. Boston: Academic Press (2016). 1–75.

50. Dolensky , et al. HIGHOUTPUT concentrator. US 8,167,988 B2, (2012).

51. Sami A, Irfan M, Uddin R, Ali AH, Khan H, Khan E, et al. Oxygen concentrator design: zeolite based pressure swing adsorption In: *IEEC 2022*. Basel Switzerland: MDPI (2022). 26.

52. Zhu X, Liu Y, Yang X, Liu W. Study of a novel rapid vacuum pressure swing adsorption process with intermediate gas pressurization for producing oxygen. *Adsorption*. (2017) 23:175–84. doi: 10.1007/s10450-016-9843-4

53. Ackley MW. Medical oxygen concentrators: a review of progress in air separation technology. *Adsorption*. (2019) 25:1437–74. doi: 10.1007/s10450-019-00155-w

54. Stoppa F, Scordari F, Mesto E, Sharygin V, Bortolozzi G. Calcium-aluminum-silicate-hydrate "cement" phases and rare Ca-zeolite association at Colle Fabbri, Central Italy. *Central Eur J Geosci*. (2010) 2:175–87. doi: 10.2478/v10085-010-0007-6

55. Hamed HH. Oxygen separation from air using zeolite type 5A. *Al-Qadisiyah Journal for Engineering Sciences*. (2015) 8:147–158.

56. Vemula RR, Urich MD, Kothare MV. Experimental design of a "snap-on" and standalone single-bed oxygen concentrator for medical applications. *Adsorption*. (2021) 27:619–28. doi: 10.1007/s10450-021-00299-8

57. Blakeman TC, Rodriquez D, Britton TJ, Johannigman JA, Petro MC, Branson RD. Evaluation of oxygen concentrators and chemical oxygen generators at altitude and temperature extremes. *Mil Med*. (2016) 181:160–8. doi: 10.7205/MILMED-D-15-00130

58. Arora A, Hasan MMF. Flexible oxygen concentrators for medical applications. *Sci Rep*. (2021) 11:14317 doi: 10.1038/s41598-021-93796-3

59. Gurkin VN, Kagramanov GG, Loiko A, Farnosova EN, Blanko-Pedrekhon AM, Milyaev AV. Development of a portable membrane oxygen concentrator. *Membr Membr Technol*. (2021) 3:186–91. doi: 10.1134/S2517751621030045

60. Gould GA, Scott W, Hayhurst MD, Flenley DC. Technical and clinical assessment of oxygen concentrators. *Thorax*. (1985) 40:811–6. doi: 10.1136/thx.40.11.811

61. Ackley MW. Medical oxygen concentrators: a review of progress in air separation technology. *Adsorption*. (2019) 25:1437–74. doi: 10.1007/s10450-019-00155-w

62. Evans TW, Waterhouse J, Howard P. Clinical experience with the oxygen concentrator. *Br Med J (Clin Res Ed)*. (1983) 287:459–61. doi: 10.1136/bmj.287.6390.459

63. Hardavella G, Karampinis I, Frille A, Sreter K, Rousalova I. Oxygen devices and delivery systems. *Breathe*. (2019) 15:e108:–e116. doi: 10.1183/20734735.0204-2019

64. Dakkak J, Tang W, Smith JT, Balasubramanian A, Mattson M, Ainechi A, et al. Burden and unmet needs with portable oxygen in patients on long-term oxygen therapy. *Ann Am Thorac Soc*. (2021) 18:1498–505. doi: 10.1513/AnnalsATS.202005-487OC

65. Möller S, Ivarsson B, Nordström LÅ, Johansson A. Ltot patients' experience of a portable oxygen unit and health-related quality of life—a cross-sectional study. *Healthcare (Switzerland)*. (2020) 8:8. doi: 10.3390/healthcare8020182

66. Matito-Martos I, García-Reyes J, Martin-Calvo A, Dubbeldam D, Calero S. Improving ammonia production using zeolites. *J Phys Chem C*. (2019) 123:18475–81. doi: 10.1021/acs.jpcc.9b05366

67. Rodriquez DJ, Blakeman TC, Dorlac W, Johannigman JA, Branson RD. Maximizing oxygen delivery during mechanical ventilation with a portable oxygen concentrator. *J Trauma Acute Care Surg*. (2010) 69:S87–93. doi: 10.1097/TA.0b013e3181e44b27

68. Rees PJ, Dudley F. Provision of oxygen at home. *BMJ*. (1998) 317:935–8. doi: 10.1136/bmj.317.7163.935

69. Ritz RH, Previtera JE. Oxygen Supplies During a Mass Casualty Situation. *Respir Care*. (2008) 53:215–24.

70. Pollock NW, Natoli MJ. Chemical oxygen generation: evaluation of the green dot systems, inc portable, nonpressurized emOx device. *Wilderness Environ Med*. (2010) 21:244–9. doi: 10.1016/j.wem.2010.04.008

71. McCoy RW. Options for home oxygen therapy equipment: storage and metering of oxygen in the home. *Respir Care*. (2013) 58:65–85. doi: 10.4187/respcare.01932

72. Duke T, Peel D, Graham S, Howie S, Enarson PM, Jacobson R. Oxygen concentrators: a practical guide for clinicians and technicians in developing countries. *Ann Trop Paediatr*. (2010) 30:87–101. doi: 10.1179/146532810X12637745452356

73. Yáñez AM, Prat JP, Álvarez-Sala JL, Calle M, Díaz Lobato S, Gonzalez JLG, et al. Oxygenation with a single portable pulse-dose oxygen-conserving device and combined stationary and portable oxygen delivery devices in subjects with COPD. *Respir Care*. (2015) 60:382–7. doi: 10.4187/respcare.03470

74. Katz I, Pichelin M, Montesantos S, Kang MY, Sapoval B, Zhu K, et al. An in silico analysis of oxygen uptake of a mild COPD patient during rest and exercise using a portable oxygen concentrator. *Int J COPD*. (2016) 11:2427–34. doi: 10.2147/COPD.S112473

75. Chen JZ, Katz IM, Pichelin M, Zhu K, Caillibotte G, Noga ML, et al. Comparison of pulsed versus continuous oxygen delivery using realistic adult nasal airway replicas. *Int J COPD*. (2017) 12:2559–71. doi: 10.2147/COPD.S141976

76. Myers S, Dinga P, Anderson M, Schubert C, Mlotha R, Phiri A, et al. Use of bubble continuous positive airway pressure (bCPAP) in the management of critically ill children in a Malawian paediatric unit: an observational study. *BMJ Open Respir Res*. (2019) 6:e000280. doi: 10.1136/bmjresp-2018-000280

77. Branson RD. Oxygen therapy in copd. *Respir Care*. (2018) 63:734–48. doi: 10.4187/respcare.06312

78. Melani AS, Sestini P, Rottoli P. Home oxygen therapy: re-thinking the role of devices. *Expert Rev Clin Pharmacol*. (2018) 11:279–89. doi: 10.1080/17512433.2018.1421457

79. Chen JZ, Katz IM, Pichelin M, Zhu K, Caillibotte G, Finlay WH, et al. In vitro–in silico comparison of pulsed oxygen delivery from portable oxygen concentrators versus continuous flow oxygen delivery. *Respir Care*. (2019) 64:117–29. doi: 10.4187/respcare.06359

80. Martin DC. Contemporary portable oxygen concentrators and diverse breathing behaviours-a bench comparison. *BMC Pulm Med*. (2019) 19:19. doi: 10.1186/s12890-019-0980-x

81. Alises SM, Caneiras C, Díaz-Lobato S. A telephone-based survey of current trends, habits and beliefs in patients receiving portable oxygen therapy in Madrid, Spain. *ERJ Open Res*. (2019) 5:5. doi: 10.1183/23120541.00059-2018

82. Litch JA, Bishop RA. Oxygen concentrators for the delivery of supplemental oxygen in remote high-altitude areas. *Wilderness Environ Med*. (2000) 11:189–91. doi: 10.1580/1080-6032(2000)011[0189:OCFTDO]2.3.CO;2

83. Sardesai I, Grover J, Garg M, Nanayakkara PB, di Somma S, Paladino L, et al. Short term home oxygen therapy COVID-19 patients: the COVID-HOT algorithm. *J Fam Med Primary Care*. (2020) 9:3209–19. doi: 10.4103/jfmpc.jfmpc_1044_20

84. Shen C, Yue X, Wang J, Shi C, Li W. Nocturnal oxygen therapy as an option for early COVID-19. *Int J Infect Dis*. (2020) 98:176–9. doi: 10.1016/j.ijid.2020.06.080

85. Leonard-Duke J, Evans S, Hannan RT, Barker TH, Bates JHT, Bonham CA, et al. Multi-scale models of lung fibrosis. *Matrix Biol*. (2020) 91-92:35–50. doi: 10.1016/j.matbio.2020.04.003

86. Cuerpo S, Palomo M, Hernández-González F, Francesqui J, Albacar N, Hernández C, et al. Improving home oxygen therapy in patients with interstitial lung diseases: application of a noninvasive ventilation device. *Ther Adv Respir Dis*. (2020) 14:175346662096302. doi: 10.1177/1753466620963027

87. Cheah PK, Steven EM, Ng KK, Hashim MI, Abdul Kadir MH, Roder NP. The use of dual oxygen concentrator system for mechanical ventilation during COVID-19 pandemic in Sabah, Malaysia. *Int J Emerg Med*. (2021) 14:30. doi: 10.1186/s12245-021-00354-9

88. Pulsan F, Duke T. Response to oxygen therapy using oxygen concentrators run off solar power in children with respiratory distress in remote primary health facilities in Papua New Guinea. *Trop Dr*. (2021) 51:15–9. doi: 10.1177/0049475520947886

89. Madaan N, Paul BC, Guleria R. Meeting oxygen requirements of rural India: a self-contained solution. *Indian J Public Health*. (2021) 65:82–4. doi: 10.4103/ijph.IJPH_1405_20

90. Yadav VK, Suriyaprabha R, Inwati GK, Gupta N, Singh B, Lal C, et al. A noble and economical method for the synthesis of low cost zeolites from coal fly ash waste. *Adv Mater Process Technol*. (2021) 8:301–319. doi: 10.1080/2374068X.2021.1927640

91. Kianfar E. Zeolites: properties, applications, modification and selectivity. *Advances in Research and Applications*. ed. A. Mahler (NY, USA: Nova Science Publishers, Inc.) (2020) 1–29.

92. Pan M, Omar HM, Rohani S. Application of nanosize zeolite molecular sieves for medical oxygen concentration. *Nano*. (2017) 7:7. doi: 10.3390/nano7080195

93. Modi S, Inwati GK, Gacem A, Saquib Abullais S, Prajapati R, Yadav VK, et al. Nanostructured antibiotics and their emerging medicinal applications: an overview of nanoantibiotics. *Antibiotics*. (2022) 11:708. doi: 10.3390/antibiotics11060708

94. Yadav VK, Choudhary N, Khan SH, Malik P, Inwati GK, Suriyaprabha R, et al. "Synthesis and characterisation of nano-biosorbents and their applications for waste water treatment," in *Handbook of Research on Emerging Developments and Environmental Impacts of Ecological Chemistry*. (Gujurat, India: IGI Global Publisher) (2020), 252–290. doi: 10.4018/978-1-7998-1241-8

95. Gnanamoorthy G, Yadav VK, Yadav KK, Ramar K, Alam J, Shukla AK, et al. Fabrication of different SnO_2 nanorods for enhanced photocatalytic degradation and antibacterial activity. *Environ Sci Pollut Res*. (2021):1–11. doi: 10.1007/s11356-021-13627-w

96. Gnanamoorthy G, Ramar K, Ali D, Yadav VK, Kumar G. Synthesis and effective performance of Photocatalytic and antimicrobial activities of Bauhinia tomentosa Linn plants using of gold nanoparticles. *Opt Mater (Amst)*. (2022) 123:111945. doi: 10.1016/j.optmat.2021.111945

97. Malik P, Inwati GK, Mukherjee TK, Singh S, Singh M. Green silver nanoparticle and Tween-20 modulated pro-oxidant to antioxidant curcumin transformation in aqueous CTAB stabilized peanut oil emulsions. *J Mol Liq*. (2019) 291:111252. doi: 10.1016/j.molliq.2019.111252

98. Kumar Inwati G, Kumar P, Roos WD, Swart HC. Thermally induced structural metamorphosis of ZnO:Rb nanostructures for antibacterial impacts. *Colloids Surf B: Biointerfaces*. (2020) 188:110821. doi: 10.1016/j.colsurfb.2020.110821

99. Inwati GK, Kumar P, Singh M, Yadav VK, Kumar A, Soma VR, et al. Study of photoluminescence and nonlinear optical behaviour of AgCu nanoparticles for nanophotonics. *Nano-Struct Nano-Objects*. (2021) 28:100807. doi: 10.1016/j.nanoso.2021.100807

100. Kim MZ, Alam SF, Arepalli D, Rehman AU, Choi WY, Cho CH. Prevention in thermal crack formation in chabazite (CHA) zeolite membrane by developing thin top zeolite and thick intermediate layers. *Nano*. (2021) 12:11. doi: 10.3390/nano11082113

101. Yadav VK, Singh B, Choudhary N. Characterization of Indian incense stick powders for their physical, chemical and mineralogical properties. *World J Environ Biosci*. (2020) 9:39–43.

102. Inwati GK, Yadav VK, Ali IH, Vuggili SB, Kakodiya SD, Solanki MK, et al. 2D personality of multifunctional carbon nitrides towards enhanced catalytic performance in energy storage and remediation. *Appl Sci (Switzerland)*. (2022) 12, 3753–3569. doi: 10.3390/app12083753

103. Ho Y-S. Review of second-order models for adsorption systems. *J Hazard Mater*. (2006) 136:681–9. doi: 10.1016/j.jhazmat.2005.12.043

104. Inwati GK, Kumar P, Singh M, Yadav VK, Kumar A, Soma VR, et al. Study of photoluminescence and nonlinear optical behaviour of AgCu nanoparticles for nanophotonics. *Nano-Structures Nano-Objects*. (2021) 28:100807. doi: 10.1016/j.nanoso.2021.100807

105. Yadav VK, Choudhary N, Ali D, Gnanamoorthy G, Inwati GK, Almarzoug MHA, et al. Experimental and computational approaches for the structural study of novel Ca-rich zeolites from incense stick ash and their application for wastewater treatment. *Adsorpt Sci Technol*. (2021) 2021:1–12. doi: 10.1155/2021/6066906

106. Yadav VK, Inwati GK, Ali D, Gnanamoorthy G, Bera SP, Khan SH, et al. Remediation of azure a dye from aqueous solution by using surface-modified coal Fly ash extracted Ferrospheres by mineral acids and toxicity assessment. *Adsorpt Sci Technol*. (2022) 2022:1–14. doi: 10.1155/2022/7012889

107. Paital B, Das K, Parida SK. Inter nation social lockdown versus medical care against COVID-19, a mild environmental insight with special reference to India. *Sci Total Environ*. 728:138914. doi: 10.1016/j.scitotenv.2020.138914

108. Paital B. Nurture to nature via COVID-19, a self-regenerating environmental strategy of environment in global context. *Sci Total Environ*. (2020) 729:139088. doi: 10.1016/j.scitotenv.2020.139088

109. Das K, Paital B. First week of social lockdown versus medical care against COVID-19 – with special reference to India. *Curr Trend Biotechnol Pharmacol*. (2020) 14:196–216. doi: 10.5530/ctbp.2020.2.20

110. Paital B, Agrawal PK. Air pollution by NO2 and PM2.5 explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. *Environ Chem Lett*. (2020) 19:25–42. doi: 10.1007/s10311-020-01091-w

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 June 2023
DOI 10.3389/fmed.2023.1209977

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Habib Md Reazaul Karim,
All India Institute of Medical Sciences, Raipur, India
Hui-Ling Lin,
Chang Gung University, Taiwan

*CORRESPONDENCE
Zongan Liang
✉ liangza@scu.edu.cn
He Yu
✉ yuhe@wchscu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 21 April 2023
ACCEPTED 19 May 2023
PUBLISHED 09 June 2023

CITATION
Ni Z, Zhou Y, Tang N, Yu H and Liang Z (2023) Comparison of actual performance in humidification among different high-flow nasal cannula devices: a bench study.
Front. Med. 10:1209977.
doi: 10.3389/fmed.2023.1209977

Comparison of actual performance in humidification among different high-flow nasal cannula devices: a bench study

Zhong Ni†, Yuyan Zhou†, Na Tang, He Yu* and Zongan Liang*

Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: The physiological effects of HFNC devices are closely related to temperature and humidity. HFNC devices from different manufacturers may have varied performances. It is unclear whether there are differences in the humidification performance of different HFNC devices and the degree of differences.

Methods: Four integrated HFNC devices (AIRVO 2, Fisher & Paykel Healthcare, Auckland, New Zealand; TNI softFlow 50, TNI Medical AG, Würzburg, Germany; HUMID-BH, RESPIRACARE, Shenyang, China; OH-70C, Micomme, Hunan, China) and a ventilator with an HFNC module (bellavista 1000, Imtmedical, Buchs, Switzerland) were evaluated using their matching circuits. The dew point temperature was set at 31, 34, and 37°C (set-DP). In MR850, it was set to non-invasive mode (34°C/−3°C) and invasive mode (40°C/−3°C), respectively. At each level of set-DP, the flow was set from 20L/min up to its maximum set limit at a gradient of 5L/min or 10L/min. After stabilization, the dew point temperature, temperature, relative humidity, and flow rate of the delivered gas from the cannulas were recorded.

Results: There were significant differences in actual-DP among these devices at any set-DP (p<0.001). The actual-DP of OH-70C and TNI softFlow 50 was lower than set-DP, and the difference between the actual-DP and the set-DP of these two devices increased with the increase of set-DP. AIRVO 2, bellavista 1000 (MR850), and HUMID-BH can provide the nominal humidity at 37°C. The actual-DP increased with the increase of set-flow under each set-DP in AIRVO 2, TNI softFlow 50 and bellavista 1000 (MR850), but decreased when the set-flow was greater than 60L/min. The actual-T of the delivered gas was higher than actual-DP in all devices and was higher than set-DP in AIRVO 2 and HUMID-BH.

Conclusion: Set-flow, set-DP, and types of devices will affect the actual temperature and humidity of the delivered gas. AIRVO 2, bellavista 1000 (MR850), and HUMID-BH can provide the nominal humidity at 37°C and may be more suitable for tracheotomy patients. The flow rate over 60L/min should be set with caution.

KEYWORDS

high-flow nasal cannula, flow, humidity, dew point temperature, temperature

1. Introduction

High-flow nasal cannula (HFNC) oxygen therapy can deliver high flow oxygenated gas ranging from 10 to 80 L/min in adults with the gas adequately heated and humidified. A stable fraction of inspired oxygen (FiO_2) of 21–100% can be achieved by such a flow. Furthermore, the high flow rate of HFNC can generate positive end-expiratory pressure (PEEP) (1, 2), wash out anatomic dead space in upper airways (3), and decrease the work of breathing (4). Besides, an appropriate gas temperature and humidity can reduce airway contraction, improve mucus-ciliary clearance system function and promote secretion clearance (5), which is another tremendous advantage of HFNC. Dry or poorly humidified medical gases may reduce epithelial cell function, increase inflammation, and cause dry nose, pharynx, and nasal pain, which can provoke respiratory tract spasms and increase airway resistance (6–9). The use of HFNC can prevent nasal epistaxis (5, 6). HFNC has been widely concerned as a non-invasive respiratory support alternative in critically ill patients as many studies have proved that HFNC has some advantages over conventional oxygen therapy (COT) and non-invasive ventilation (NIV) (10–13). A recent study confirmed that HFNC could improve the dyspnea score and mucus production in acute exacerbation of chronic obstructive pulmonary disease patients (14). Furthermore, the heat and humidification delivered by HFNC help to maintain hydration and mobilize secretions, which positively affect the mucus hypersecretion of patients with COVID-19 (15).

There are many kinds of HFNC devices on the market, including high-flow air oxygen mixer systems, air entrainment systems, and integrated HFNC devices (16). In addition, some manufacturers have added HFNC modules for ventilators. To reduce condensation, most HFNC devices were equipped with servo-controlled heating wires to the circuit. However, condensation cannot be avoided entirely. The international standard for HFNC devices (ISO/DIS 80601-2-90) was recently published and updated by the International Organization for Standardization (17). This document addresses the basic safety and essential performance requirements of respiratory high-flow therapy equipment. The absolute humidity must not be lower than 16 mg/L (or equivalent to 90% relative humidity at 22°C) for use via nasal cannulas and shall not be lower than 33 mg/L for use in patients with upper respiratory tract bypass. The output gas of the humidifier should not exceed 43°C to avoid being burned. The differences in the length, position, and shape of the heating wire may end up in different outputs under identical settings, which might affect the clinical assessment. A previous study related to heat and moisture exchangers showed that manufacturer specifications and bedside measurements of absolute humidity differed considerably for the Hygroster, which did not achieve efficient humidification in certain instances (18). So, an independent assessment is required. A few studies in this field explored how parameter settings affect humidification performance, condensation, and patient tolerance in models and human volunteers (19–23).

According to previous studies, flow plays a vital role in the humidification performance of HFNC (24–27). This study aims to explore the characteristics and limits of humidification performance among different devices in real ward environment by measuring actual-T and humidity at the nasal cannulas under various flow settings. This study may help clinicians with a profound understanding of the differences between actual output and set parameters, as well as the differences between different HFNC devices. Moreover, the results may provide a basis for the selection and parameter setting of different devices.

2. Materials and methods

We tested four integrated HFNC devices (AIRVO 2, Fisher & Paykel Healthcare, Auckland, New Zealand; TNI softFlow 50, TNI Medical AG, Würzburg, Germany; HUMID-BH, RESPIRACARE, Shenyang, China; OH-70C, Micomme, Hunan, China) and a ventilator with an HFNC module (bellavista 1000, Imtmedical, Buchs, Switzerland) using their matching heating circuits, humidification chambers, nasal cannulas, and other accessories. The devices were provided by the West China Hospital's Medical Intensive Care Unit (MICU) and have been used stably in the clinic without fault. Figure 1 shows the detailed information and appearance of the devices and heating circuits.

A multi-function measuring instrument ALMEMO ®2,390-8 with a fixed digital hygrometer FNAD46-3 was used to measure the temperature, dew point, and relative humidity of actually delivered gas.

2.1. Preparations

As shown in Figure 2, the cannulas were connected to the measuring instrument, so the target parameters at the nasal plug are measured directly using the same adapter as the study (28).

The measurement was carried out in an independent ward (4 m long, 3 m wide, and 2.5 m height, with no strong air convection) in the MICU of West China Hospital. The ambient temperature was controlled, and all equipment that might interfere with the test was removed from the ward. All HFNC devices and measuring instruments were fully preheated and calibrated before measurement. During the testing process, the ambient temperature was 22.1 ± 0.7C, the relative humidity was 74 ± 7%, and the atmospheric pressure was 716.9 ± 5.1 mmHg.

2.2. Protocol

The dew point or dew point temperature of a gas is the temperature at which the water vapor contained in the gas is transformed into a liquid state. The water vapor contained in the gas exists as a liquid below the dew point temperature, while a gaseous component is above the dew point temperature. For example, the dew point temperature of 20°C can be equated with absolute humidity 16 mg/L (minimum requirements of the ISO standard) at standard atmospheric pressure. So, the dew point or dew point temperature is an indicator of absolute humidity, and three of the tested devices (AIRVO 2, TNI softFlow 50, and HUMID-BH) take the dew point temperature as the temperature setting target. Therefore, we choose the dew point temperature to reflex the humidification ability of the devices.

The dew point temperature was set at 31, 34, and 37°C, named set-DP. In MR850, it was set to non-invasive mode (34°C /−3°C) and invasive mode (40°C/−3°C), respectively. At each level of set-DP, the flow was set at 20, 25, 30, 35, 40, 45, 50, 60, 70, and 80 L/min, depending on their maximum flow, which was named set-flow. The FiO_2 was fixed at 21%.

The dew point temperature, temperature, relative humidity, and flow rate of the delivered gas from the cannulas were named actual-DP,

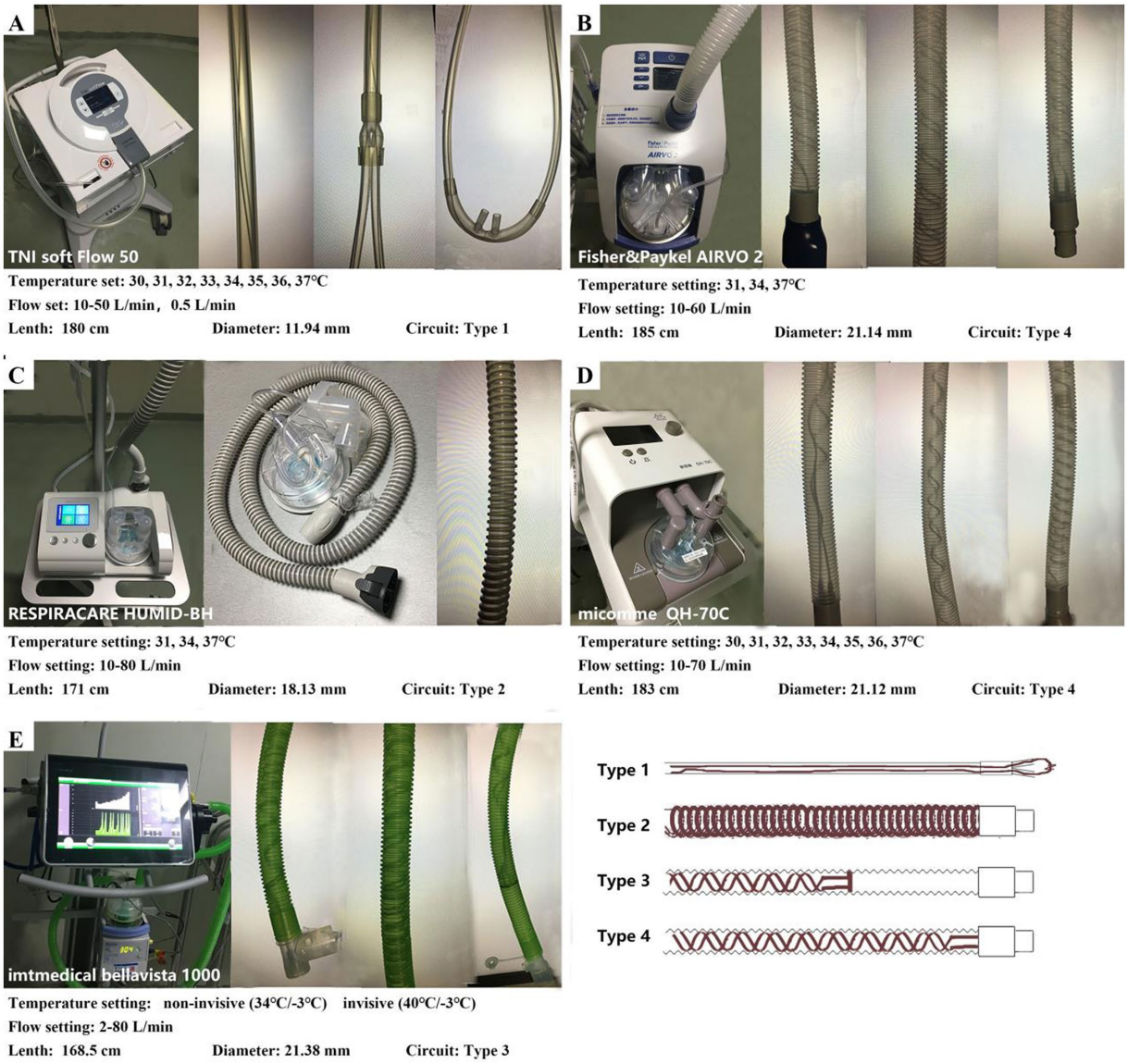


FIGURE 1
Settings of the HFNC devices and characteristics of the circuits. **(A)** TNI softFlow 50: The diameter of the circuit is smaller than other devices, and the heating wire is straight and runs through the whole circuit and the nasal cannulas (Type 1). **(B,D)** AIRVO 2 and OH-70C: the heating wire is arranged in a double helix structure in the whole circuit (Type 4). **(C)** HUMID-BH: The heating wire is wrapped in a spiral shape outside the circuit (Type 2). **(E)** Bellavista 1000 (MR850): the heating wire is arranged in a double helix structure in the circuit and located approximately 3/4 of the circuit near the humidifier (Type 3). Temperature sensors are installed both at the chamber outlet and the end of the heating circuit to provide feedback on the temperature and humidity output of MR850 in real time.

actual-T, actual-RH, and actual-flow. For each setting, after stabilization for 15 min, actual-DP and actual-flow were recorded three times at an interval of 10 s, respectively. The test was repeated with set-flow increasing and decreasing orders to reduce the influence of heat accumulation. And then all the testing processes were repeated twice at different date to reduce disturbance from possible environmental factors and avoid contingency.

2.3. Statistics

Finished testing for normality, nonnormally distributed variables are expressed as medians (interquartile range), and normally distributed variables are expressed as the mean ± SD. Kruskal-Wallis H test was used to compare the effect of different set-flow on actual-T and actual-DP in a single device. Kruskal-Wallis H test was also used to compare actual parameters in different systems with the same settings. Wilcoxon signed rank test was used to compare differences between settings and actual parameters. The statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS statistical software.

3. Results

There was no significant difference in actual-T and actual-DP between the flow-increasing and the flow-decreasing setting groups ($p = 0.117$ and 0.325). The test order and the running time of the

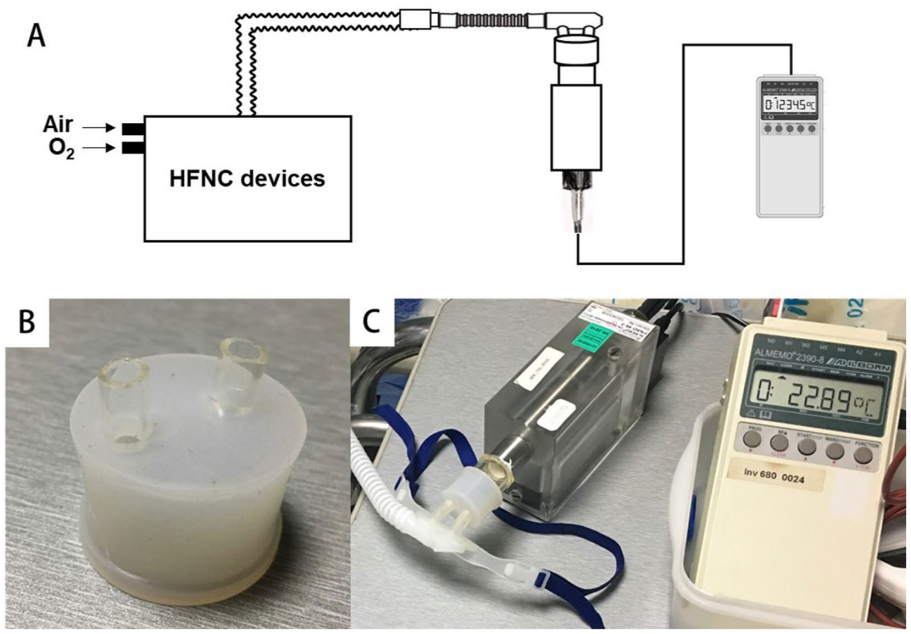


FIGURE 2
Connect the cannulas to the digital hygrometer via a special adapter. **(A,C)** The schematic diagram and real scene of the connection between the equipment and the hygrometer. **(B)** The special adapter.

TABLE 1 Characteristics of actual-DP in five devices.

Devices	Actual-DP (°C)		
	Set-DP: 31°C	Set-DP: 34°C	Set-DP: 37°C
AIRVO 2	31.94 (31.43, 32.25)	34.71 (34.08, 35.14)	37.00 (36.88, 37.31)*
TNI softFlow 50	30.28 ± 0.22	32.48 (32.24, 32.77)	33.98 (33.63, 34.27)
HUMID-BH	30.51 (30.08, 30.90)	31.85 (31.41, 33.75)	37.72 ± 0.36
OH-70C	30.17 ± 0.34	31.14 (30.96, 31.35)	33.22 (32.81, 33.43)
Bellavista 1000 (MR850)	32.10 (30.98, 32.43)	N/A	36.47 (35.73, 36.95)

The data are presented as the median (IQR) or mean ± SD. *There was no significant difference between the actual-DP and the corresponding set-DP ($p = 0.134$).

devices do not affect actual-T and humidification efficiency. The following analysis no longer considers the test order.

3.1. Difference between actual-DP and set-DP in a single device and different devices

Actual-DP of the five devices in the real ward environment was summarized in Table 1. There were significant differences in actual-DP among these devices at any set-DP ($p < 0.001$). Besides, there were significant differences between actual-DP and the set-DP of all the tested device ($p < 0.001$) except for AIRVO 2 when the dew point was set at 37°C (Table 1). Table 1 and Figure 3 showed that the deviation of the actual-DP of OH-70C and TNI softFlow 50 increased with increasing set-DP. Actual-DP of these two devices was lower than the corresponding set-DP and was considerably lower when the dew point was set at 37°C. AIRVO 2, bellavista 1000 (MR850), and HUMID-BH can provide enough humidity at set-DP 37°C.

3.2. Influence of set-flow on actual-DP in a single device

There is no difference between actual-DP and the set-DP in AIRVO 2 when set-flow 35–45 L/min at set-DP 37°C. In other devices, there were significant differences in actual-DP at different set-flow rates under the same set-DP ($p < 0.001$). Except for bellavista 1000 (MR850) at set-DP 31°C, there was a significant correlation between actual-DP and set-flow in all devices at the same set-DP ($p < 0.001$). Under each set-DP, actual-DP in AIRVO 2 and TNI softFlow 50 showed an increasing trend with increased set-flow. Actual-DP in bellavista 1000 (MR850) increased with the rise of set-flow when set-flow was lower than 60 L/min and decreased with the increase of set-flow when it exceeded 60 L/min.

3.3. Actual-T and actual-RH in a single device and different systems

The actual-T and actual-RH of the five devices in the real ward environment were summarized in Tables 2, 3 and Figure 4. The actual-T of bellavista1000 (MR850) was close to the set-DP when set-flow below 60 L/min. When set-flow was higher than 60 L/min, the difference between the actual-T and set-DP increased with increasing

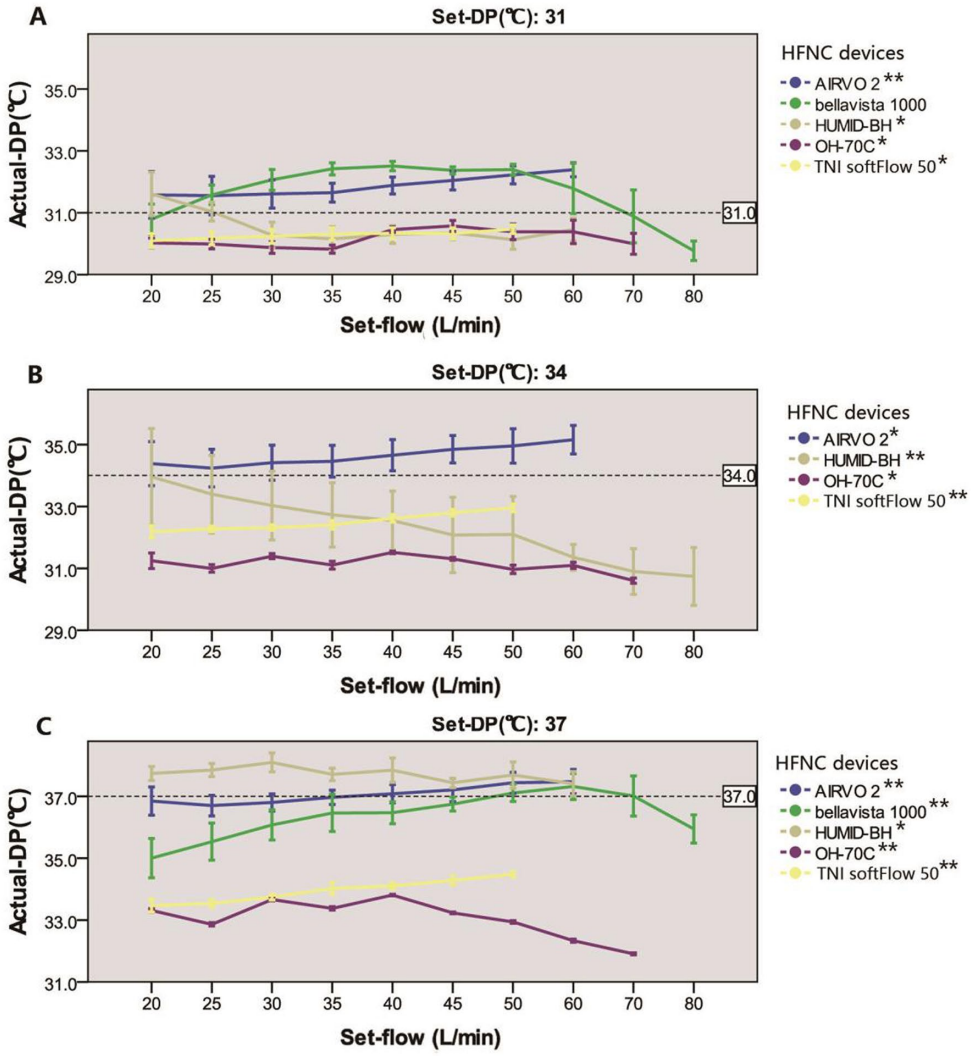


FIGURE 3
Relationship between actual-DP and set-flow levels in five devices at set-DP 31°C **(A)**, 34°C **(B)**, and 37°C **(C)**. *There was a significant correlation between actual-DP and the set-flow at this set-DP (p<0.001). The correlation coefficient was between 0.3 and 0.5; **The correlation coefficient was larger than 0.5. The error line represents the standard deviation.

TABLE 2 Characteristics of actual-T in five devices.

Devices	Actual-T (°C)		
	Set-DP: 31°C	Set-DP: 34°C	Set-DP: 37°C
AIRVO 2	33.23 (33.08, 33.37)	36.20 (36.01, 36.61)	38.93 (38.75, 39.13)
TNI softFlow 50	34.21 (33.68, 34.77)	34.53 (34.32, 34.91)	35.16 (35.03, 35.27)
HUMID-BH	33.81 (33.33, 34.13)	35.98 (35.72, 36.14)	39.43 (38.95, 39.77)
OH-70C	30.92 (30.51, 31.32)	32.61 (32.25, 32.96)	34.57 (34.33, 34.80)
Bellavista 1000 (MR850)	32.36 (32.06, 32.61)		36.90 (36.27, 37.25)

The data are presented as the median (IQR) or mean ± SD.

set-flow. Bellavista1000 (MR850) can provide the target actual-T and the highest actual-RH.

By contrast, the actual-T of the integrated HFNC devices was generally higher than set-DP, while the actual-DP was lower than set-DP. The actual-T of HUMID-BH could reach 39.43(38.95, 39.77) °C when the dew point was set at 37°C.

4. Discussion

In this study, the actual output of five devices under different settings was quantitatively analyzed. The results showed that actual-T and dew point varied depending on the set-DP, set-flow, and the devices. In addition, three points are worth noting: (1) AIRVO 2, bellavista 1000 (MR850), and HUMID-BH can provide the target humidity, especially when the dew point temperature was set at 37°C, (2) However, OH-70C and TNI softFlow 50 cannot provide the

10.3389/fmed.2023.1209977

TABLE 3 Characteristics of actual-RH in five devices.

Devices	Actual-RH		
	Set-DP:31°C	Set-DP:34°C	Set-DP:37°C
AIRVO 2	90.4% ± 3.2%	89.6% ± 2.3%	88.7% ± 1.4%
TNI softFlow 50	75.3% (74.0, 78.3%)	86.7% ± 2.3%	92.6% (90.4, 94.3%)
HUMID-BH	79.2% (77.5, 81.5%)	75.0% (72.9, 85.4%)	90.3% (85.9, 94.5%)
OH-70C	95.2% (93.4, 96.2%)	90.5% (87.0, 93.1%)	91.4% (88.3, 93.0%)
Bellavista 1000 (MR850)	98.4% (97.5, 98.9%)		98.2% (97.9, 98.7%)

The data are presented as the median (IQR) or mean ± SD.

actual-DP exceeding 34°C, and (3) The actual-T of OH-70C and TNI softFlow 50 was significantly lower than the set-DP.

AIRVO 2, TNI softFlow 50, and bellavista 1000 (MR850) all present that the actual-DP increases with the increase of set-flow. The integrated HFNC devices optimize the cooperative control of temperature, humidity, and flow output, which can automatically adjust the power of the heating plate according to set-flow, so as to ensure the appropriate humidification effect and avoid the occurrence of insufficient or excessive humidification. MR850 monitors the temperature at the outlet of the humidification chamber and the end of the heating circuit in real time, and the feedback circuit controls the power of the heating plate and heating wire to maintain a stable temperature and humidity output. Several studies on AIRVO 2 and MR850 have obtained the same results (23, 25, 29). Plotniko et al. (27) reported that the best performance for all flows in terms of AH was found with the Fisher & Paykel MR850 HH, regardless of the circuit used. According to their analysis, in addition to the corresponding increase in heating power, when the set-flow increases, the heat exchange time between the gas and the ambient is shorter, so the condensation loss is less and the humidity is higher.

The actual-DP of bellavista 1000 (MR850) decreased with the increase of set-flow when set-flow was greater than 60 L/min. Actual-DP of HUMID-BH decreased obviously with the increase of flow rate when the dew point was set at 34°C (the flow rate of HUMID-BH can only be set to 60–80 L/min when DP is set at 34°C due to the limit of the device). The gas passes over a heated water chamber faster at a higher flow rate (>60 L/min) and the insufficient power of the heating humidifier may lead to a decline in humidification efficiency. Chikata et al. (23) monitored the electrical output of the heating plate of MR850 using View850 (Fisher & Paykel). It was proved that the output power of the heating plate was less than 100% when the flow was set at 20 and 40 L/min. When the flow was set at 60 L/min, the electric output of the heating plate was maintained at 100%, and the temperature at the outlet of the humidifier and at the end of the circuit was lower than set. A study on the humidification efficiency of HFNC at a higher flow rate (60–100 L/min) confirmed the same results that traditional heating humidifiers could not provide sufficient humidification at 60–100 L/min (24). Plotnikow et al. (27) got the same results. On the other hand, previous studies showed that when the patient's inspiratory flow exceeded the HFNC flow, the absolute humidity of the inhaled gas was affected by tidal volume (25). Meanwhile, studies have shown that a higher flow rate (60 L/min) can improve patients' comfort with severe hypoxemia (30). Another study on healthy volunteers confirmed they preferred flow delivered at 30 or 40 mg H_2O/L (19). Therefore, the heating and humidification of higher flow rate gas still deserves attention and needs to be improved.

The actual-T of independent HFNC devices was higher than the corresponding actual-DP and was higher than the set-DP in some devices. The actual-T of bellavista 1000 (MR850) is similar to the corresponding actual-DP. Accordingly, the condensation of bellavista 1000 (MR850) was remarkable. To minimize condensation, manufacturers usually set the heating wire temperature 2–3°C higher than the set-DP. When set to invasive mode (40°C/−3°C), the MR850 humidifier will heat the gas to 37°C and relative humidity 100% at the outlet of the humidification chamber. Then the gas will be heated to 40°C in the heating circuit and maintained at 40°C during transportation (relative humidity<100%). The temperature sensors and servo-control system achieve the stable temperature and humidity output of MR850 (Figure 1E). When it reaches the nasal cannulas section (without heating guide wire), the gas will be cooled to 37°C and RH100% again at the nasal cannulas. Independent HFNC device also adopts such a design. However, the temperature of the heating wire might be too high to cool down to the target temperature due to the lack of servo-control. At this time, the humidity of the delivered gas is unsaturated, and condensation is not easy to occur, which is consistent with the observed results in the study. But there is a problem that the comfort of patients may be reduced. Chikata et al. explored the influence of room temperature and the covering length of the heating wire on condensation. They found that reducing the internal and external temperature difference of the circuit and increasing the length of the heating guide wire can reduce condensation effectively (29, 31). According to the characteristics of the circuit, the actual-T of TNI softFlow 50 (small diameter and straight heating wire in the whole circuit and the nasal cannulas, Figure 1A) should be the highest among the five devices tested theoretically. But the results show that actual-T was 34.21 (33.68–34.77), 34.53(34.32–34.91) and 35.16(35.03–35.27) °C, respectively, when DP was set at 31,34,37°C. In OH-70C (double helix heating wire in the whole circuit, Figure 1D), the actual-T was lower than set-DP. In HUMID-BH (heating wire wrapped outside the circuit, Figure 1C), the actual-T was the actual highest, which might be related to the slow heat dissipation. The circuit characteristics of the five devices tested in this study are not significantly related to the heating and humidification efficiency. The working power and the algorithm of the devices are the main factors that affect this result, in addition to the circuit structure. So, the advantages and disadvantages of different structures cannot be compared, and further research is needed.

The high temperature of gas delivered by HFNC devices is one of the reasons why patients do not tolerate HFNC treatment. A previous study found that patients who failed HFNC had a higher incidence of discomfort 1 h after initiation (32), suggesting that the comfort may be related to clinical outcomes. However, the optimum humidity and temperature of HFNC are still controversial. The default setting of 37°C can achieve the best humidification efficiency. But there is no evidence to prove that 37°C is the best for HFNC because of the retained humidification function of the upper respiratory tract. The results of this study show that actual-T in most devices is relatively higher than set-DP, and the setting of 37°C might not be conducive to patient comfort. At present, no studies have provided evidence for the effect of actual-T of HFNC on patients' comfort. Only a short time (20 min) cross-test was

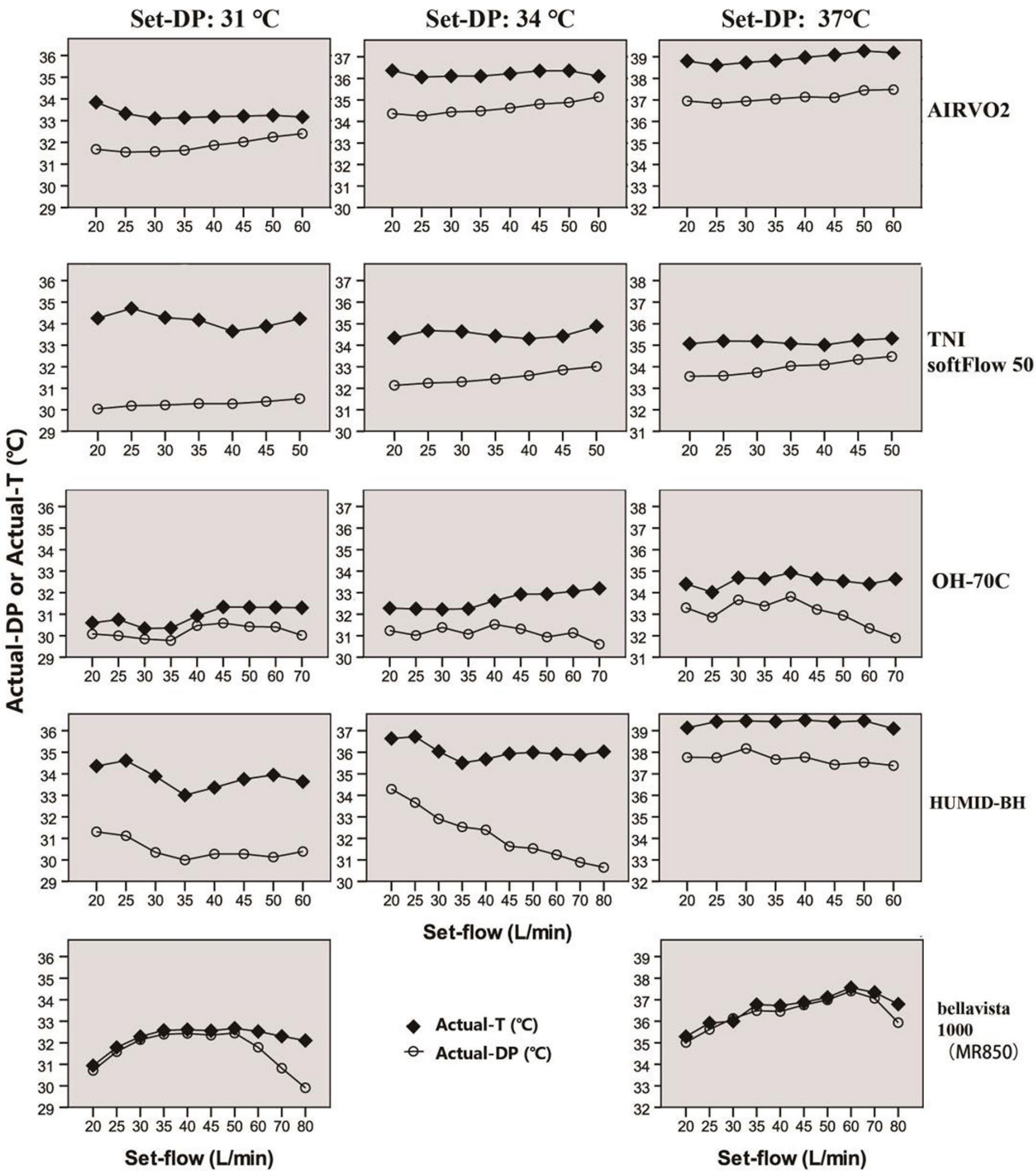


FIGURE 4
Actual-T and actual-DP of five devices at different set-flow levels under different set-DPs.

conducted concerning the set-DP, and the results showed that the lower set temperature was related to higher comfort (30). The study also claimed that the results were highly heterogeneous.

This study provides data for evaluating the actual performance of HFNC devices in the real ward environment. The differences between set values and actual values exist objectively, and more bench and clinical studies are needed to determine and quantify the consequences of these differences. Increasing the number of devices to be tested, improving the airway model and spontaneous breathing simulation in bench studies, or conducting clinical tests on healthy volunteers or representative patients are all essential directions in future research.

This study has several limitations. Firstly, the result can only represent the actual output under the specific environmental conditions in this study, and it may change in different environments. Secondly, we only tested one device from each manufacturer, and there are inevitably individual differences. Thirdly, although all the tests we conducted in a single room which did not have strong air convection and were controlled by an air conditioning system, it was

impossible to maintain absolutely constant ambient temperature and humidity, which may also affect the results of the tests.

5. Conclusion

Set-flow, set-DP, and types of devices will affect the actual temperature and humidity of the delivered gas. And there is a deviation from the nominal output with uncertain clinical consequences. AIRVO 2, bellavista 1000 (MR850), and HUMID-BH can provide the nominal humidity at 37°C and may be more suitable for tracheotomy patients. The flow rate over 60 L/min should be set with caution, in which situation both the built-in heating humidifier in HFNC devices and the traditional independent heating humidifier failed to provide sufficient humidity. The actual-T of the delivered gas is higher than actual-DP or set-DP, which may cause the patient discomfort.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ZN and YZ designed the study, drafted the manuscript, and conducted the literature search and data analysis, contributing equally to the study. NT assisted with experiments and manuscript preparation. ZL and HY revised the manuscript critically for important intellectual content, and gave the final version for publication. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to thank Li Ling (Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University) for valuable advice regarding methodology.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. *Respir Care*. (2015) 60:1369–76. doi: 10.4187/respcare.03814

2. Yao JJ, Peng MM, Zou GH, He KX, Ma DD. Effects of flow on carbon dioxide washout and nasal airway pressure in healthy adult volunteers during the constant-flow mode in a non-invasive ventilator. *Chin Med J*. (2020) 133:2515–7. doi: 10.1097/CM9.0000000000001079

3. Moller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, et al. Nasal high flow reduces dead space. *J Appl Physiol*. (2017) 122:191–7. doi: 10.1152/japplphysiol.00584.2016

4. Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, et al. Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. *Intensive Care Med*. (2017) 43:1453–63. doi: 10.1007/s00134-017-4890-1

5. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest*. (2015) 148:253–61. doi: 10.1378/chest.14-2871

6. Nishimura M. High-flow nasal cannula oxygen therapy in adults: physiological benefits, indication, clinical benefits, and adverse effects. *Respir Care*. (2016) 61:529–41. doi: 10.4187/respcare.04577

7. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. *J Appl Physiol*. (1996) 81:1739–43. doi: 10.1152/jappl.1996.81.4.1739

8. Fontanari P, Zattara-Hartmann MC, Burnet H, Jammes Y. Nasal eupnoeic inhalation of cold, dry air increases airway resistance in asthmatic patients. *Eur Respir J*. (1997) 10:2250–4. doi: 10.1183/09031936.97.10102250

9. Chidekel A, Zhu Y, Wang J, Mosko JJ, Rodriguez E, Shaffer TH. The effects of gas humidification with high-flow nasal cannula on cultured human airway epithelial cells. *Pulm Med*. (2012) 2012:380686. doi: 10.1155/2012/380686

10. Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med*. (2020) 46:2226–37. doi: 10.1007/s00134-020-06312-y

11. Zhu Y, Yin H, Zhang R, Ye X, Wei J. High-flow nasal cannula oxygen therapy versus conventional oxygen therapy in patients after planned extubation: a systematic review and meta-analysis. *Crit Care*. (2019) 23:180. doi: 10.1186/s13054-019-2465-y

12. Cortegiani A, Longhini F, Carlucci A, Scala R, Groff P, Bruni A, et al. High-flow nasal therapy versus noninvasive ventilation in COPD patients with mild-to-moderate hypercapnic acute respiratory failure: study protocol for a noninferiority randomized clinical trial. *Trials*. (2019) 20:450. doi: 10.1186/s13063-019-3514-1

13. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. *JAMA*. (2020) 323:1839–41. doi: 10.1001/jama.2020.4914

14. Crimi C, Noto A, Cortegiani A, Campisi R, Heffler E, Gregoretti C, et al. High flow nasal therapy use in patients with acute exacerbation of COPD and bronchiectasis: a feasibility study. *COPD*. (2020) 17:184–90. doi: 10.1080/15412555.2020.1728736

15. Crimi C, Pierucci P, Renda T, Pisani L, Carlucci A. High-flow nasal cannula and COVID-19: a clinical review. *Respir Care*. (2022) 67:227–40. doi: 10.4187/respcare.09056

16. Nishimura M. High-flow nasal cannula oxygen therapy devices. *Respir Care*. (2019) 64:735–42. doi: 10.4187/respcare.06718

17. ISO. Medical electrical equipment — Part 2–90: particular requirements for basic safety and essential performance of respiratory high-flow therapy equipment: ISO 80601-2-90:2021 [S/OL], [2023-05-18]. (2021) Available at: https://www.iso.org/standard/80858.html.

18. Thiery G, Boyer A, Pigne E, Salah A, De Lassence A, Dreyfuss D, et al. Heat and moisture exchangers in mechanically ventilated intensive care unit patients: a plea for an independent assessment of their performance. *Crit Care Med*. (2003) 31:699–704. doi: 10.1097/01.CCM.0000050443.45863.F5

19. Delorme M, Bouchard PA, Simard S, Lellouche F. Hygrometric performances of different high-flow nasal cannula devices: bench evaluation and clinical tolerance. *Respir Care*. (2021) 66:1720–8. doi: 10.4187/respcare.09085

20. Harduin C, Allaouchiche B, Negre J, Goy-Thollot I, Barthelemy A, Fougeray A, et al. Impact of flow and temperature on non-dyspnoeic dogs' tolerance undergoing high-flow oxygen therapy. *J Small Anim Pract*. (2021) 62:265–71. doi: 10.1111/jsap.13284

21. Narang I, Carberry JC, Butler JE, Gandevia SC, Chiang AKI, Eckert DJ. Physiological responses and perceived comfort to high-flow nasal cannula therapy in

awake adults: effects of flow magnitude and temperature. *J Appl Physiol*. (2021) 131:1772–82. doi: 10.1152/japplphysiol.00085.2021

22. Reiner E, Stein N, Rotschild A, Gashi T, Bibi H, Waisman D. Using heated humidified high-flow nasal cannulas for premature infants may result in an underestimated amount of water reaching the airways. *Acta Paediatr*. (2021) 110:1475–82. doi: 10.1111/apa.15675

23. Chikata Y, Unai K, Izawa M, Okuda N, Oto J, Nishimura M. Inspiratory tube condensation during high-flow nasal cannula therapy: a bench study. *Respir Care*. (2016) 61:300–5. doi: 10.4187/respcare.04331

24. Chikata Y, Morinishi K, Nishimura M. Humidification in very-high-flow nasal-cannula therapy in an adult lung model. *Respir Care*. (2019) 64:809–17. doi: 10.4187/respcare.06417

25. Chikata Y, Izawa M, Okuda N, Itagaki T, Nakataki E, Onodera M, et al. Humidification performance of two high-flow nasal cannula devices: a bench study. *Respir Care*. (2014) 59:1186–90. doi: 10.4187/respcare.02932

26. Ullrich TL, Czernik C, Buhrer C, Schmalisch G, Fischer HS. Differential impact of flow and mouth leak on oropharyngeal humidification during high-flow nasal cannula: a neonatal bench study. *World J Pediatr*. (2018) 14:305–9. doi: 10.1007/s12519-018-0138-6

27. Plotnikow GA, Villalba D, Gogniat E, Quiroga C, Pérez Calvo E, Scapellato JL. Performance of different active humidification Systems in high-flow Oxygen Therapy. *Respir Care*. (2020) 65:1250–7. doi: 10.4187/respcare.07654

28. Zhou Y, Ni Z, Ni Y, Liang B, Liang Z. Comparison of actual performance in the flow and fraction of inspired O2 among different high-flow nasal cannula devices: a bench study. *Can Respir J*. (2021) 2021:6638048–10. doi: 10.1155/2021/6638048

29. Chikata Y, Ohnishi S, Nishimura M. Humidity and inspired oxygen concentration during high-flow nasal cannula therapy in neonatal and infant lung models. *Respir Care*. (2017) 62:532–7. doi: 10.4187/respcare.05319

30. Mauri T, Galazzi A, Binda F, Masciopinto L, Corcione N, Carlesso E, et al. Impact of flow and temperature on patient comfort during respiratory support by high-flow nasal cannula. *Crit Care*. (2018) 22:120. doi: 10.1186/s13054-018-2039-4

31. Chikata Y, Imanaka H, Onishi Y, Ueta M, Nishimura M. Humidification during high-frequency oscillation ventilation is affected by ventilator circuit and ventilatory setting. *Paediatr Anaesth*. (2009) 19:779–83. doi: 10.1111/j.1460-9592.2009.03068.x

32. Frat JP, Ragot S, Coudroy R, Constantin JM, Girault C, Prat G, et al. Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. *Crit Care Med*. (2018) 46:208–15. doi: 10.1097/ccm.0000000000002818

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 24 July 2023
DOI 10.3389/fmed.2023.1135570

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Hong Weng,
Wuhan University, China
Heng Gan,
British Columbia Children's Hospital, Canada

*CORRESPONDENCE
Kuang-Ming Liao
✉ abc8870@yahoo.com.tw
Shyh-Ren Chiang
✉ Chiangsr@gmail.com

†These authors have contributed equally to this work

RECEIVED 01 January 2023
ACCEPTED 23 June 2023
PUBLISHED 24 July 2023

CITATION
Feng I-J, Lin J-W, Lai C-C, Cheng K-C, Chen C-M, Chao C-M, Wang Y-T, Chiang S-R and Liao K-M (2023) Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis. *Front. Med.* 10:1135570. doi: 10.3389/fmed.2023.1135570

Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis

I-Jung Feng[1†], Jia-Wei Lin[2†], Chih-Cheng Lai[3], Kuo-Chen Cheng[4,5], Chin-Ming Chen[6,7], Chien-Ming Chao[8], Ying-Ting Wang[9], Shyh-Ren Chiang[4,10*] and Kuang-Ming Liao[11*]

[1]Institute of Precision Medicine, National Sun Yat-sen University, Kaohsiung, Taiwan, [2]Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan, [3]Division of Hospital Medicine, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan, [4]Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan, [5]Department of Safety, Health, and Environmental Engineering, Chung Hwa University of Medical Technology, Tainan, Taiwan, [6]Departments of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan, [7]Recreation and Health-Care Management, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, [8]Department of Intensive Care Medicine, Chi Mei Medical Center, Liouying, Taiwan, [9]Departments of Respiratory Therapy, Chi Mei Medical Center, Tainan, Taiwan, [10]Department of General Education, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, [11]Department of Internal Medicine, Chi Mei Medical Center, Chiali, Taiwan

Objectives: We assessed the efficacies of various corticosteroid treatments for preventing postexubation stridor and reintubation in mechanically ventilated adults with planned extubation.

Methods: We searched the Pubmed, Embase, the Cochrane databases and ClinicalTrial.gov registration for articles published through September 29, 2022. Only randomized controlled trials (RCTs) that compared the clinical efficacies of systemic corticosteroids and other therapeutics for preventing postextubation stridor and reintubation were included. The primary outcome was postextubation stridor and the secondary outcome was reintubation.

Results: The 11 assessed RCTs reported 4 nodes: methylprednisolone, dexamethasone, hydrocortisone, and placebo, which yielded 3 possible pairs for comparing the risks of post extubation stridor and 3 possible pairs for comparing the risks of reintubation. The risk of postextubation stridor was significantly lower in dexamethasone- and methylprednisolone-treated patients than in placebo-treated patients (dexamethasone: OR = 0.39; 95% CI = 0.22–0.70; methylprednisolone: OR = 0.22; 95% CI = 0.11–0.41). The risk of postextubation stridor was significantly lower in methylprednisolone-treated patients than in hydrocortisone-treated: OR = 0.24; 95% CI = 0.08–0.67) and dexamethasone-treated patients: OR = 0.55; 95% CI = 0.24–1.26). The risk of reintubation was significantly lower in dexamethasone- and methylprednisolone-treated patients than in placebo-treated patients: (dexamethasone: OR = 0.34; 95% CI = 0.13–0.85; methylprednisolone: OR = 0.42; 95% CI = 0.25–0.70). Cluster analysis showed that dexamethasone- and methylprednisolone-treated patients had the lowest risks of stridor and reintubation. Subgroup analyses of patients with positive cuff-leak tests showed similar results.

Conclusions: Methylprednisolone and dexamethasone were the most effective agents against postextubation stridor and reintubation.

KEYWORDS

dexamethasone, hydrocortisone, methylprednisolone, network meta-analysis, postextubation stridor, reintubation

Introduction

Endotracheal intubation is a common procedure for critically ill patients with acute respiratory failure that requires mechanical ventilation (MV) in an intensive care unit (ICU) or for patients under general anesthesia undergoing surgery in the operating room. Although endotracheal intubation is usually uneventful, it can lead to tracheal rupture, pneumothorax or pneumomediastinum, tongue necrosis, or soft palate injury (1–5). Laryngeal edema is another complication of endotracheal intubation, and it might be a cause of postextubation stridor and subsequent reintubation (6). Most important, laryngeal edema-associated extubation failure can prolong an ICU or hospital stay, increase mortality and morbidity, and add to medical costs. Thus, it is important to avoid laryngeal edema-associated postextubation stridor and reintubation failure.

Several interventions—parenterally administering corticosteroids, nebulizing epinephrine, and administering an inhaled helium/oxygen mixture—have been developed to prevent postextubation stridor and reintubation (6). Corticosteroids are supposed to reduce both inflammation and edema, and to exert their effect on preventing postextubation stridor and reintubation. Moreover, several meta-analyses (7–9) have shown that administering prophylactic corticosteroids before planned extubation significantly reduced the incidence rates of postextubation stridor and reintubation in adults. In studies that used methylprednisolone, dexamethasone, hydrocortisone, and placebo (10–19), however, corticosteroid anti-inflammation potencies differed. No prior study has specifically compared these four interventions. We hypothesized that different corticosteroids would have different effects against postexubation stridor and reintubation. Therefore, we did this network meta-analysis to assess the efficacies of these interventions.

Methods

Study search and selection

This network meta-analysis (NMA) was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement (20). The protocol of this study was prospectively registered at PROSPERO (registration number: CRD42022362888). All clinical studies were identified in a systematic review of the literature through September 29, 2022 in the Pubmed, Embase, the Cochrane databases and ClinicalTrial.gov registration. We used the following search terms: "intubation," "intratracheal," "laryngeal edema," "airway obstruction," "stridor," "post extubation larynx* edema*," steroid*," "corticosteroid*," 'glucocorticoid*," "prednisone," "prednisolone," "methylprednisolone," "dexamethasone," "cortisone," "hydrocortisone," and "adult" (Appendix 1). Only randomized clinical trials (RCTs) that compared the efficacy of systemic corticosteroid treatments and other interventions against postextubation stridor and reintubation in MV adults scheduled for extubation were included. We also searched for additional eligible studies in the reference lists of retrieved articles and relevant meta-analyses. To avoid bias, two reviewers (CCL and JWL) independently searched and examined publications. Any discrepancies were judged and determined by third author (IJF).

Data extraction

The following data were extracted from every included study: year of publication, study design, sample size, gender ratio, treatment regimens of corticosteroids and other interventions, cumulative doses (mg), frequency of administration, and incidence rates of postextubation stridor and reintubation. For RCTs that used medians and interquartile ranges as measures of central tendency and dispersion, we estimated means and standard deviations (SDs) (21).

Definitions and outcomes

The primary outcome was overall postextubation stridor and reintubation. Subgroup analyses of patients with positive cuff-leak tests were also performed.

Quality assessments

The quality of the analyzed RCTs and the risk of bias were assessed using the Cochrane Risk of Bias Assessment tool (22). We assessed seven quality domains: sequence generation, allocation concealment, participant masking, personnel masking, outcome assessor masking, incomplete outcome data, and reporting bias. Other biases were also assessed. Finally, we judged the quality of each domain as (a) low risk of bias, (b) unclear risk of bias, or (c) high risk of bias.

Statistical methods

We used STATA 15.0 (StataCorp, College Station, TX, USA), R (version 4.2.1) and R package "netmeta" to do a frequentist network

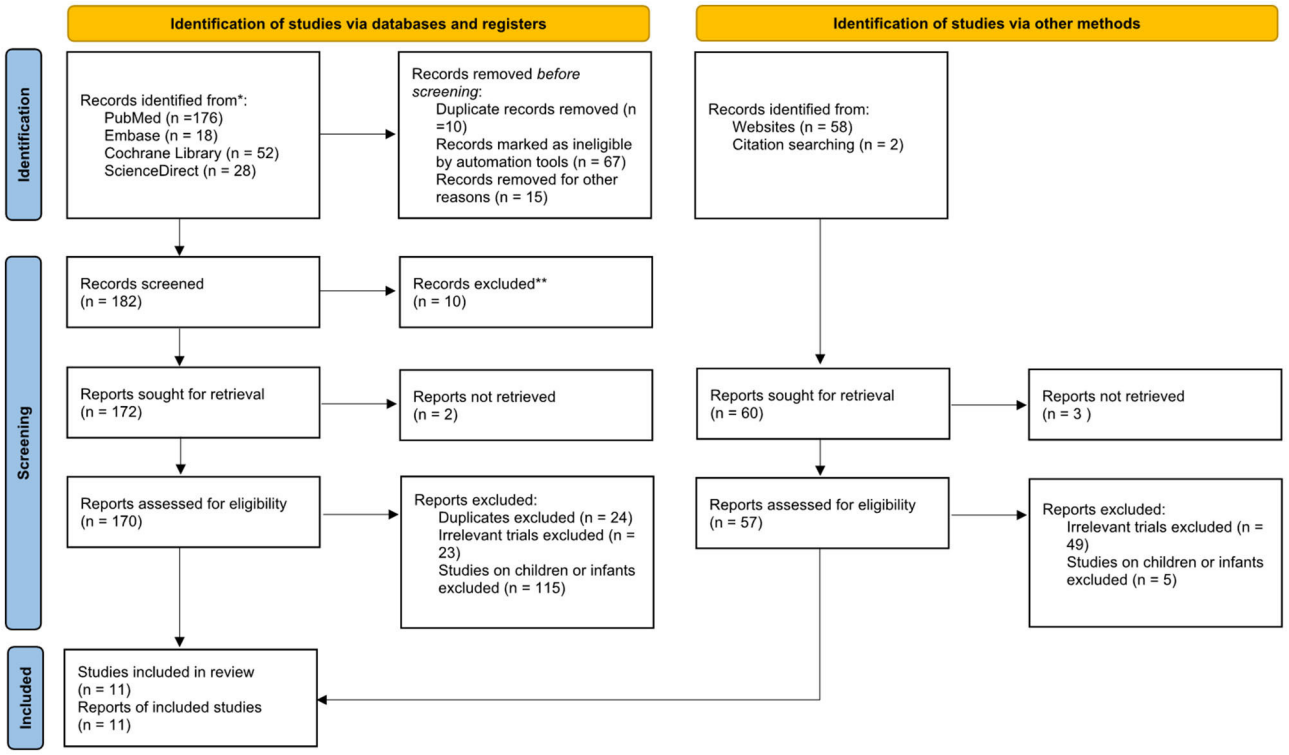


FIGURE 1
The algorithm of study selection.

meta-analysis (23). Because of the diversity of the task-related characteristics of the included RCTs, we used a random-effects model. The heterogeneity variable of all comparisons was assumed to be a single τ^2 value. The required property of transitivity was also assumed.

We used a design-by-treatment interaction model for global tests and side-splitting model for local tests to evaluate inconsistencies between direct and indirect evidence. Network plots show direct comparisons of investigated outcomes, and odds ratios (ORs) and 95% confidence intervals (95% CIs) show network effect-size estimates of pairwise comparisons.

A surface under the cumulative ranking curve (SUCRA) presents the likely rank order of each investigated treatment. To evaluate the joint ranking of postextubation stridor and reintubation both clinical outcomes, cluster analysis was performed. The optimal number of resulting cluster was defined by having maximum intra-cluster similarity and minimize inter-cluster similarity (24). Finally, we assessed publication bias using Egger's test.

Results

Search results and characteristics of the included studies

We initially identified 308 studies. After excluding 44 duplicate articles, 264 articles were screened, 135 of which were excluded on the basis of the title and abstract. After excluding study on non-adult patients (n = 135), non-RCT (n = 30), the 99 remaining articles underwent a full-text review to assess their eligibility. Finally, a total of eleven RCTs (10–19, 25) fulfilled the inclusion criteria were selected for our network meta-analysis (Figure 1; Table 1). Six RCTs (11, 12, 16–19) were done in Taiwan, three (13–15) in France, one (25) in India, and one (10) in Pakistan. Six RCTs (10–12, 17–19) used the cuff leak test (CLT) to select high-risk patients. Dexamethasone was the most commonly used corticosteroid ($n = 5$), (10, 13, 17, 18, 25) then methylprednisolone ($n = 4$), (11, 12, 14, 15) and, finally, hydrocortisone ($n = 2$) (16, 19). Follow-up observation durations were 24 h (13, 14, 16, 25) and 48 h (10–12, 17, 18). Routes of administration, doses, and frequencies of administration differed (Appendix 2). Four studies (11, 13, 15, 16) used one injection before extubation, but five studies (10, 12, 17–19) used corticosteroid for 24 h before extubation. One RTC (25) intravenously injected one group of patients with dexamethasone and treated another group with nebulized budesonide 1 h before the scheduled extubation, and then every 12 h for 48 h after the extubation.

Network meta-analysis

Among enrolled studies, four reported nodes were methylprednisolone, dexamethasone, hydrocortisone and placebo, resulting in 3 possible pairs for comparing the risks of post extubation stridor and 3 possible pairs for comparing the

TABLE 1 Characteristics of included studies.

Study/year	Location	Inclusion criteria	Study duration	Pretest with Cuff leak test	Sample Size (% of female)	Age, mean ± SD	Corticosteroid Regimen	Comparator	Observation period after extubation (h)
Gaussorgues et al. (15)	France	1. Tracheal intubation	1985/9–1986/8	–	276 (65.22)	54.00 ± 24.55	Methylprednisolone	NR	NR
Darmon et al. (13)	France	1. Tracheal intubation	1986/11–1987/11	–	700 (42.14)	53.15 ± 19.54	Dexamethasone	placebo	24
Ho et al. (16)	Taiwan	1. Intubation≥24 h and 2. Met the weaning criteria	1990/3/1–1990/8/31	–	77 (23.38)	62.48 ± 16.10	Hydrocortisone	N/S	24
Cheng et al. (12)	Taiwan	1. ≥18 yrs of age 2. intubation≥24 hrs 3. CLV%<24% 4. Met the weaning criteria	2002/2–2004/7	+	127 (62.20)	66.15 ± 16.58	Methylprednisolone	N/S	48
Francois et al. (14)	France	1. ≥18 yrs of age 2. MV≥36 h	2001/3– 2002/1	–	761 (36.40)	62.25 ± 20.69	Methylprednisolone	Isotonic saline	24
Lee et al. (17)	Taiwan	1. ≥18 years of age. 2. MV >48 h 3. CLV≤110 ml 4. Met the weaning criteria	2004/10–2006/3	+	80 (82.50)	72.55 ± 14.26	Dexamethasone	Placebo	48
Shih et al. (26)	Taiwan	1. MV ≥ 24 h 2. Met the weaning criteria 3. CLV < 110 ml	NR	+	98 (44.90)	NR	Hydrocortisone	N/S	NR
Malhotra et al. (25)	India	1. MV≥24 h 2. Met the weaning criteria and first extubation	2003/1–2006/2	–	60 (46.67)	32.90 ± 14.14	Dexamethasone	Placebo or saline	24
Baloch et al. (10)	Pakistan	1. ≥18 years of age. 2. MV≥48 h 3. CLV≤110 ml	2006/8–2008/7	+	92 (44.57)	39.65 ± 12.65	Dexamethasone	N/S	48
Cheng et al. (11)	Taiwan	1. ≥18 yrs of age 2. intubation≥4 h 3. Met the weaning criteria 4. CLT<24%	NR	+	71 (77.46)	60.49± 16.74	Methylprednisolone	N/S	48
Lin et al. (27)	Taiwan	1. ≥18 yrs of age 2. MV≥48hrs 3. CLV<110ml 4. Met the weaning criteria	2007/4/1–2010/3/31	+	126 (78.57)	74.09 ± 11.80	Dexamethasone	N/S	48

NR, not reported; CLT, cuff leak test; MV, mechanical ventilation; CLV, cuff leak volume; N/S, normal saline.

10.3389/fmed.2023.1135570

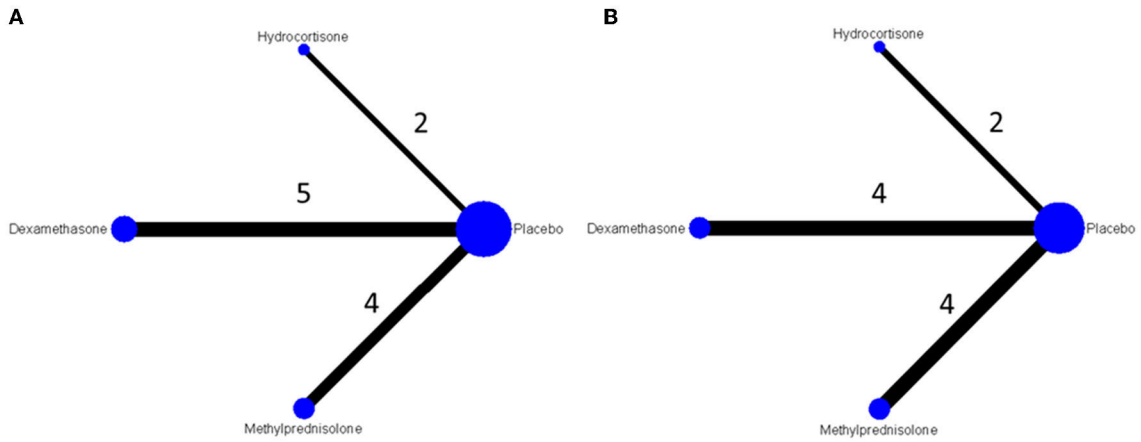


FIGURE 2
Network plot for preventive effect of **(A)** postextubation stridor and **(B)** reintubation.

risks of reintubation. Most comparisons with direct evidence are from dexamethasone or methylprednisolone and placebo. Regarding the risk of postextubation stridor, five studies compared the effects between dexamethasone and placebo. Four and one studies used methylprednisolone and hydrocortisone as study agents, respectively (Figure 2A). Regarding the risk of reintubation, each four studies compared the effect between dexamethasone or methylprednisolone and placebo. Two studies used compared hydrocortisone with placebo (Figure 2B).

Quality of studies

The risk of bias in each domain of each study was low (Figure 3). Control group in Gaussorhues et al.'s study (15) received nothing. This was hard to prevent participants and experimenters to keep unaware the group assignment during study period. High risks were marked in the bias evaluation report. Because no closed-loop was formed for the network of collected postextubation stridor-related literature, inconsistency was not examined here; however, the literature showed a significant publication bias (Egger's test: $p = 0.013$). In contrast, there was no publication bias (Egger's test: $p = 0.623$) in the collected reintubation-related literature.

Postextubation stridor risk

NMAs showed that the risk of postextubation stridor was significantly lower in dexamethasone- and methylprednisolone-treated patients than in placebo-treated patients (dexamethasone: OR: 0.39; 95% CI: 0.22-0.70; methylprednisolone: OR: 0.22; 95% CI: 0.11-0.41) (Table 2A; Figure 4).

Reintubation risk

Compared with placebo, both dexamethasone and methylprednisolone were found significantly associated with lower risk of reintubation (dexamethasone: OR: 0.34; 95% CI: 0.13-0.85; methylprednisolone: OR: 0.42; 95% CI: 0.25-0.70) (Table 2B; Figure 5).

Ranked order of interventions

For preventing postextubation stridor, methylprednisolone had the largest surface under the cumulative ranking curve (SUCRA) (97.6), followed by dexamethasone (66.9), hydrocortisone (21.6), and placebo (13.9). For reducing the risk of reintubation, dexamethasone had the largest SUCRA (80.7), followed by methylprednisolone (70.7), hydrocortisone (41.0), and placebo (7.6) (Figure 6). According to the SUCRA ranking outcomes, methylprednisolone and dexamethasone were considered in one with the most potent intervention cluster (Figure 6).

Subgroup analysis

For patients with positive CLTs, both dexamethasone and methylprednisolone were associated with a significantly lower risk of postextubation stridor than was placebo (dexamethasone: OR:0.26; 95% CI:0.14–0.50; SUCRA: 75.1; methylprednisolone: OR:0.26; 95% CI:0.13–0.55; SUCRA: 74.8). Moreover, both corticosteroids were associated with a significantly lower risk of reintubation than was placebo (dexamethasone: OR:0.31; 95% CI:0.10–0.94; SUCRA: 74.0; methylprednisolone: OR:0.32; 95% CI:0.14–0.69; SUCRA: 74.8) methylprednisolone, respectively.

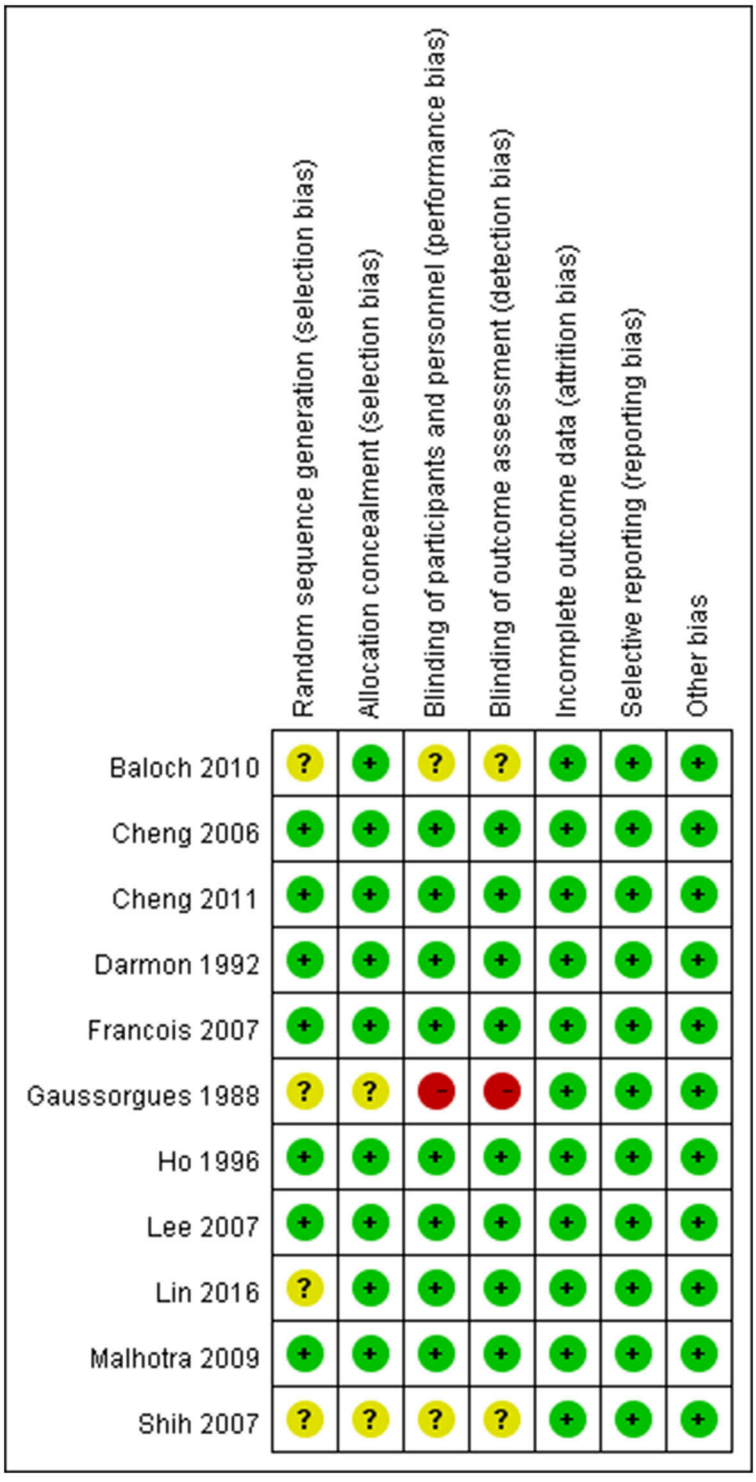


FIGURE 3
Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Discussion

This is the first network meta-analysis of 11 RCTs with a total of 2,371 patients that compare the efficacies of three commonly used corticosteroids (dexamethasone, methylprednisolone, and hydrocortisone) against postextubation stridor and reintubation in patients with a scheduled extubation. This analysis provided useful information on the choice of appropriate corticosteroid

formula for preventing postextubation stridor and reintubation in this population. Of three kinds of corticosteroid, dexamethasone and methylprednisolone were the most efficacious corticosteroids in this network meta-analysis. Methylprednisolone was ranked highest in the preventing postextubation stridor, and in contrast, hydrocortisone was ranked lowest. Regarding reintubation, dexamethasone and methylprednisolone was ranked much higher than hydrocortisone. A similar trend was observed in the subgroup analysis of high risk patients selected using cuff-leak test. Overall, this network meta-analysis also found that methylprednisolone and dexamethasone were associated with significantly lower risk of postextubation stridor and reintubation than placebo among overall population and the subgroups selected with cuff-leak test. In summary, we found that methylprednisolone and dexamethasone are the most potent kind of corticosteroids in the preventing postextubation stridor and reintubation and their prophylactic use can effectively reduce the risk of postextubation stridor and reintubation before elective extubation among patients with mechanical ventilation. In contrast, the usefulness of hydrocortisone was limited in this clinical condition. All these findings should suggest the better role of methylprednisolone and dexamethasone than hydrocortisone in this clinical entity.

TABLE 2 Preventive efficiencies for postextubation stridor (A) and reintubation (B) calculated for each pair of corticosteroids as per the results of the network meta-analyses.

(A) Postexutbation stridor			
Placebo			
1.09 (0.48,2.49)	Hydrocortisone		
2.55 (1.44,4.53)*	2.33 (0.85,6.37)	Dexamethasone	
4.65 (2.47,8.76)*	4.25 (1.49,12.10) *	1.82 (0.79,4.19)	Methylprednisolone
(B) Reintubation			
Placebo			
1.53 (0.52,4.49)	Hydrocortisone		
2.96 (1.18,7.43)*	1.93 (0.47,7.97)	Dexamethasone	
2.37 (1.43,3.94)*	1.55 (0.47,5.09)	0.80 (0.28,2.29)	Methylprednisolone

Relative effect estimates in pooled ORs and corresponding 95% CIs are displayed for 4 corticosteroids treatments. In the table, each OR represents the interaction intensity of two treatments. Cells with a * indicates a treatment above the cell has a significantly influence than the treatment shown to its right.

Our findings in this network meta-analysis can be explained by the different anti-inflammatory activities of three corticosteroids. Corticosteroids differ in their relative amount of anti-inflammatory potency. Dexamethasone and methylprednisolone have much higher anti-inflammatory potency than hydrocortisone. In general, 25 mg of hydrocortisone is equivalent to 5 mg of methylprednisolone, and 1 mg of dexamethasone according to their relative anti-inflammatory potency (28). Therefore, methylprednisolone and dexamethasone are supposed to more effectively reduce inflammatory laryngeal edema and further significantly lower the risk of postextubation stridor and reintubation than hydrocorticosone. We suggest using methylprednisolone (20 mg ever 6 h) and dexamethasone (5 mg ever 6 h) before extubation.

Our study has some limitations. First, the regimens of the corticosteroid treatments are different in the selected RCTs, which might lead to different preventive effects. Second, the number of enrolled studies is small; thus, we cannot further assess the effects of the different regimens of corticosteroids. Additional studies are needed to investigate their confounding effects. Third, some mechanisms such as publication bias and other forms of reporting bias might have impact on our interpretation of the results. Several possible confounding factors, such as sex, duration of intubation, and the size of the endotracheal tube were not assessed in this meta-analysis. There are some potential biases, heterogeneity or generalizability in meta-analyses. The meta-analysis combines the results of various types of study design to generate an overall effect size. If there are significant heterogeneities in these studies, the focus should shift from the summary effect to the dispersion itself. In addition, meta-analysis focused on the main outcomes and its

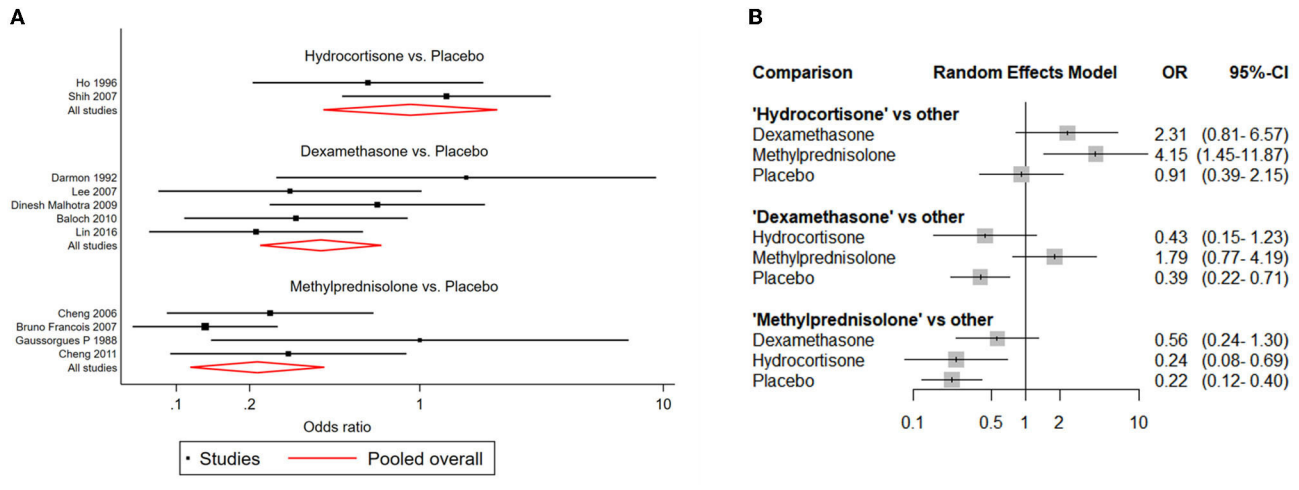


FIGURE 4
Network forest plots of postextubation stridor. **(A)** Forest plot of individual studies grouped by comparison with direct evidence. ORs and corresponding 95% CIs were displayed. **(B)** Forest plot of summarized association between different corticosteroids and risk of postextubation stridor.

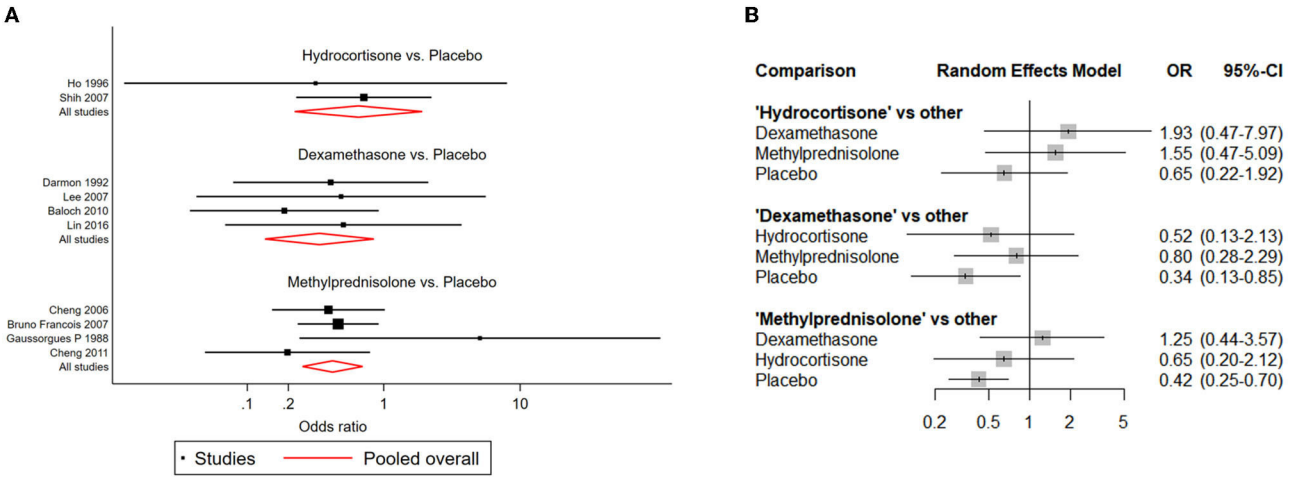


FIGURE 5
Network forest plots of reintubation. **(A)** Forest plot of individual studies grouped by comparison with direct evidence. ORs and corresponding 95% CIs were displayed. **(B)** Forest plot of summarized association between different corticosteroids and risk of reintubation.

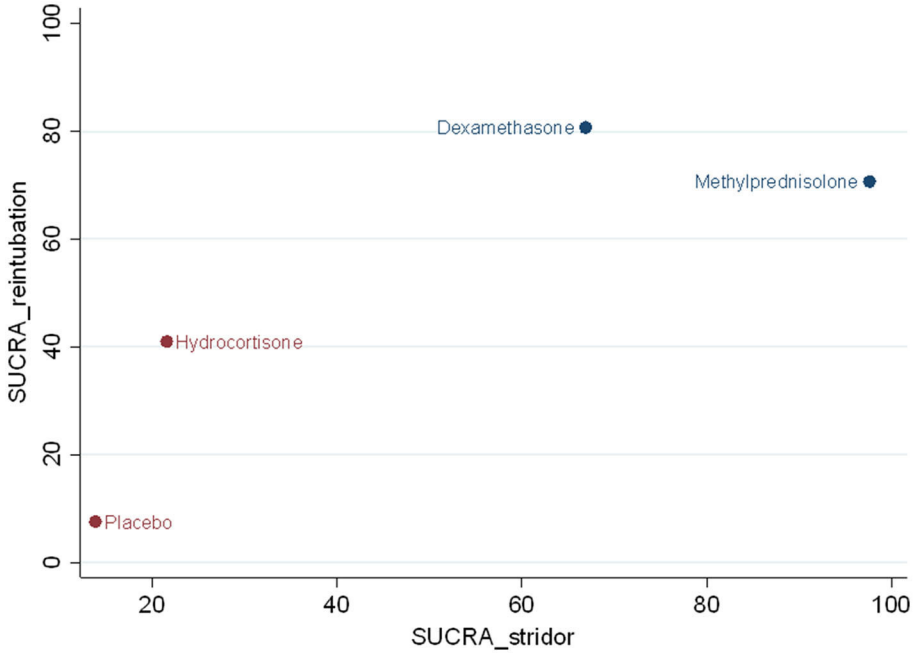


FIGURE 6
Clustered ranking plot. The SUCRA value for each agent for preventing effect of postextubation stridor and reintubation.

results can be generalizable to particular group of patients but not another.

However, we could not do a subgroup analysis because so few trials reported separate results based on sex, duration of intubation, and the size of the endotracheal tube. We did not evaluate the risk of adverse effects caused by corticosteroids.

Although the risk of corticosteroid-related complications, e.g., fluid retention, infection, gastrointestinal bleeding, and hyperglycemia are low in additional investigations are needed to assess the possibility of negative side effects. Finally, because studies were not administering equipotent doses of steroids, methylprednisolone and dexamethasone are more effective than hydrocortisone and this may be a significant confounder.

The comparison between different corticosteroids are statistical rather than direct clinical comparisons. However, we clarify the selection of studies, pre-specification of the pooled analysis, the risk of bias in each domain of each study was low and the outcome of individual studies in relation to the pooled result. We believe the validity and interpretation of pooled analyses.

Conclusion

Our findings indicate that methylprednisolone and dexamethasone are the most effective corticosteroids for preventing postextubation stridor and reintubation. Nevertheless, future large-scale clinical studies are needed to confirm our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

C-CL, C-MChe, and I-JF: concepts and design. J-WL, K-CC, S-RC, and I-JF: analysis and interpretation of data. C-MCha and C-CL: drafting of the manuscript. C-MChe, K-ML, and Y-TW: critical revision of the manuscript. I-JF: statistical analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1135570/full#supplementary-material

References

1. Khan RM, Sharma PK, Kaul N. Barotrauma: a life-threatening complication of fiberoptic endotracheal intubation in a neonate. *Paediatr Anaesth.* (2010) 20:782–4. doi: 10.1111/j.1460-9592.2010.03360.x

2. Kuhn MA, Zeitler DM, Myssiorek DJ. Tongue necrosis: a rare complication of oral intubation. *Laryngoscope.* (2010) 120 Suppl 4:S159. doi: 10.1002/lary.21623

3. Pham Q, Lentner M, Hu A. Soft palate injuries during orotracheal intubation with the videolaryngoscope. *Ann Otol Rhinol Laryngol.* (2017) 126:132–7. doi: 10.1177/0003489416678008

4. Sucato DJ, Girgis M. Bilateral pneumothoraces, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum, and subcutaneous emphysema following intubation with a double-lumen endotracheal tube for thoracoscopic anterior spinal release and fusion in a patient with idiopathic scoliosis. *J Spinal Disord Tech.* (2002) 15:133–8. doi: 10.1097/00024720-200204000-00007

5. Xu X, Xing N, Chang Y, Du Y, Li Z, Wang Z, et al. Tracheal rupture related to endotracheal intubation after thyroid surgery: a case report and systematic review. *Int Wound J.* (2016) 13:268–71. doi: 10.1111/iwj.12291

6. Wittekamp BHJ, van Mook WNKA, Tjan DHT, Zwaveling JH, Bergmans DCJJ. Clinical review: post-extubation laryngeal edema and extubation failure in critically ill adult patients. *Crit Care.* (2009) 13:233. doi: 10.1186/cc8142

7. Fan T, Wang G, Mao B, Xiong Z, Zhang Y, Liu X, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomised placebo controlled trials. *BMJ.* (2008) 337:a1841. doi: 10.1136/bmj.a1841

8. McCaffrey J, Farrell C, Whiting P, Dan A, Bagshaw SM, Delaney AP. Corticosteroids to prevent extubation failure: a systematic review and meta-analysis. *Intensive Care Med.* (2009) 35:977–86. doi: 10.1007/s00134-009-1473-9

9. Kuriyama A, Umakoshi N, Sun R. Prophylactic corticosteroids for prevention of postextubation stridor and reintubation in adults: a systematic review and meta-analysis. *Chest.* (2017) 151:1002–10. doi: 10.1016/j.chest.2017.02.017

10. Baloch R, Jakhrani N, Lal AS, Mehmood NA. Role of dexamethasone for prevention of post-extubation airway obstruction in critically ill adult patients. *J Surg Pak [International].* (2010) 15:3–8. Available online at: http://old.jsp.org.pk/Issues/JSP%2015(1)%20Jan%20March%202010/Rohina%20N%20Baloch%20OA.pdf

11. Cheng KC, Chen CM, Tan CK, Chen HM, Lu CL, Zhang H. Methylprednisolone reduces the rates of postextubation stridor and reintubation associated with attenuated cytokine responses in critically ill patients. *Minerva Anestesiol.* (2011) 77:503–9.

12. Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H. Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients. *Crit Care Med.* (2006) 34:1345–50. doi: 10.1097/01.CCM.0000214678.92134.BD

13. Darmon JY, Rauss A, Dreyfuss D, Bleichner G, Elkharrat D, Schlemmer B, et al. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone: a placebo-controlled, double-blind, multicenter study. *Anesthesiology.* (1992) 77:245–51. doi: 10.1097/00000542-199208000-00004

14. François B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial. *Lancet.* (2007) 369:1083–9. doi: 10.1016/S0140-6736(07)60526-1

15. Gaussorgues P, Boyer F, Piperno D, Gerard M, Leger P, Robert D. Do corticosteroids prevent postextubation laryngeal edema? prospective study of 276 adults. *Crit Care Med.* (1988) 16:649. doi: 10.1097/00003246-198806000-00021

16. Ho LI, Harn HJ, Lien TC, Hu PY, Wang JH. Postextubation laryngeal edema in adults. risk factor evaluation and prevention by hydrocortisone. *Intensive Care Med.* (1996) 22:933–6. doi: 10.1007/BF02044118

17. Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. *Crit Care.* (2007) 11:R72. doi: 10.1186/cc5957

18. Lee C-H, Peng M-J, Wu C-L. Comparison of high-and low-dose dexamethasone for preventing postextubation airway obstruction in adults: a prospective, randomized, double blind, placebo-controlled study. *Int J Gerontol.* (2016) 10:11–6. doi: 10.1016/j.ijge.2015.10.002

19. Cheng KC, Chen CM, Tan CK, Lin SC, Chen HM, Zhang H. Methylprednisolone reduces the incidence of postextubation stridor associated with downregulation of IL-6 in critical ill patients. *Am J Respir Crit Care Med.* (2007) 7:A593. doi: 10.1097/01.CCM.0000262548.97035.1C

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

21. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol.* (2014) 14:135. doi: 10.1186/1471-2288-14-135

22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* (2011) 343:d5928. doi: 10.1136/bmj.d5928

23. Balduzzi S, Rücker G, Nikolakopoulou A, Papakonstantinou T, Salanti G, Efthimiou O, et al. netmeta: an R package for network meta-analysis using frequentist methods. *J Stat Softw.* (2023) 106:1–40. doi: 10.18637/jss.v106.i02

24. Jung Y, Park H, Du DZ, Drake BL. A decision criterion for the optimal number of clusters in hierarchical clustering. *J Global Optimization.* (2003) 25:91–111. doi: 10.1023/A:1021394316112

25. Malhotra D, Gurcoo S, Qazi S, Gupta S. Randomized comparative efficacy of dexamethasone to prevent postextubation upper airway complications in children and adults in ICU. *Indian J Anaesth.* (2009) 53:442–9.

26. Shih CM, Chen W, Tu CY, Chen HJ, Lee JC, Tsai WK, et al. Multiple injections of hydrocortisone for the prevention of post-extubation stridor in acute respiratory failure. *Am J Respir Crit Care Med.* (2007) A593.

27. Lin CY, Cheng KH, Kou LK, Lee CH. Comparison of high-and low-dose dexamethasone for preventing postextubation airway obstruction in adults: a prospective, randomized, double blind, placebo-controlled study. *Int J Gerontol.* (2016) 10:11–6.

28. Buttgereit F, da Silva JAP, Boers M, Burmester G-R, Cutolo M, Jacobs J, et al. Standardized nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis.* (2002) 61:718–22. doi: 10.1136/ard.61.8.718

frontiers | Frontiers in Medicine

TYPE General Commentary
PUBLISHED 17 November 2023
DOI 10.3389/fmed.2023.1289321

OPEN ACCESS

EDITED BY
Zhongheng Zhang,
Sir Run Run Shaw Hospital, China

REVIEWED BY
Lei Zhao,
Capital Medical University, China

*CORRESPONDENCE
Youzhong An
✉ 2211110449@stu.pku.edu.cn

RECEIVED 05 September 2023
ACCEPTED 01 November 2023
PUBLISHED 17 November 2023

CITATION
Sun Y, Zhao H, Ma Y and An Y (2023) Commentary: Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis.
Front. Med. 10:1289321.
doi: 10.3389/fmed.2023.1289321

Commentary: Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis

Yao Sun[1], Huiying Zhao[1], Ye Ma[2] and Youzhong An[1]*

[1]Department of Critical Care Medicine, Peking University People's Hospital, Beijing, China, [2]Department of Anesthesiology, Peking University People's Hospital, Beijing, China

KEYWORDS

corticosteroids, extubation, stridor, commentary, meta-analysis

A Commentary on

Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis

by Feng, I.-J., Lin, J.-W., Lai, C.-C., Cheng, K.-C., Chen, C.-M., Chao, C.-M., Wang, Y.-T., Chiang, S.-R., and Liao, K.-M. (2023). *Front. Med.* 10:1135570. doi: 10.3389/fmed.2023.1135570

Introduction

The recent article by Feng et al. has drawn attention to the management of intubation and extubation in the field of critical care anesthesia (1). The article reviews some random control trials on the effect of different types of hormones on the prevention of post-intubation extubation stridor and reintubation. Using the PICOS principle, all relevant literature was reviewed and analyzed, then summarized for each trial. A net meta-analysis was performed to evaluate the quality of the articles and a subgroup analysis was attempted, resulting in 11 RCTs being included. The results of the study showed the superiority of using cortisol.

Discussion

In our clinical work, especially in tonsil and adenoidectomies in children, we have observed that many patients present with post-extubation stridor. So this side effect caught our attention. Through a brief literature search, we learned of the earlier and more frequent use of hormones to prevent the onset of this side effect. This team's meta-analysis of the literature did a good job of summarizing the results of the research over time and effectively demonstrated that hormones are a more effective means of relief.

TABLE 1 The review of prophylaxis of post-extubation stridor.

Intervention	Dose	Route of administration	*n*	Primary author	Age	Type of surgery and technique	Anesthetic details	Time range	Type of research	Hospital and country
Supine/ prone	/	/	242	Xiang (3)	NA	ERCP	NA	NA	A randomized controlled trial	NA
Supine/ lateral	/	/	92	Jung (4)	3–12 yr	NA	NA	NA	A randomized clinical trial	Yungpook National University; Korea
Albuterol spray	2 puffs	inhaled	120	Maddah (5)	52.34 ±8.95 yr	NA	NA	In 2021	A bouble-blind randomized clinical trial	5 Azar Educational Hospital in Gorgan; Northern Iran
Dexamethasone	8 mg TID first 24 h; 4 mg BID next 24 h	iv	110	Amoozadeh (2)	52.1±14.1 yr	Neck surgery	NA	April 2021 to July 2021	An observational prospective cohort study	Imam Khomeini Hospital's; Iran
Remifentanil/ ambroxol hydrochloride/ budesonide suspension	Remifentanil/ 0.5 μg/g; ambroxol 15 mg hydrochloride; budesonide suspension 0.5 mg	iv/ inhaled	46	Yang (6)	NA	Removing the tonsil under general anesthesia and adenoidectomy under nasal endoscope	NA	NA	A randomized clinical trial	Cangzhou Central Hospital; China
Tracheal tubes	/	/	2246	Weiss (7)	1.93 (1.48) yr in the cuffed and 1.87 (1.45) yr in the uncuffed	ENT, Head surgery, Cleft, Thoracic, Abdominal, Laparoscopy, Urology, Limb, Cardiac catheterization, Gastroenter, Radiology, and Others	NA	NA	A prospective, randomized, controlled multi-center trial	University Children's Hospital Zurich; 24 European pediatric anesthesia centers; Switzerland
Bloodletting acupuncture	/	/	60	Saghaei (8)	33.8 (18.6); 38.37 (15.5) (month)	Scheduled for elective surgery	Atropine 10 $\mu g.kg^{-1}$; Midazolam 25–100 $\mu g.kg^{-1}$; thiopental 5 $mg.kg^{-1}$; Fentanyl 1 $\mu g.kg^{-1}$; Succinylcholine 2 $mg.kg^{-1}$; halothane	NA	A double-blind, randomized trial	NA
Cuffed vs. uncuffed endotracheal intubation	/	/	40	Nishat (9)	3–10 yr	Oral surgeries,	Sevoflurane	February to December 2019	A randomized controlled study	NA

(Continued)

10.3389/fmed.2023.1289321

TABLE 1 (Continued)

Intervention	Dose	Route of administration	*n*	Primary author	Age	Type of surgery and technique	Anesthetic details	Time range	Type of research	Hospital and country
Lidocaine	topical 4 mg/kg of 2%; intravenous 1 mg/kg of 2% iv	/	134	Koç (10)	7.1 ± 1.7; 6.7 ± 1.3 yr; 7.6 ± 2.4 yr; 6.3 ± 0.8 yr	Tonsillectomy and/or adenoidectomy	Atropine, 0.015 mg/kg, meperidine, 1 mg/kg; gas mixture of N2O, O2, and halothane	NA	A randomized controlled trial	NA
Dexmedetomidine	Dexmedetomidine 2.0 μg/kg	im	100	Ambesh (11)	35.64 ± 14.93 yr; 38.08 ± 12.58 yr	Laminectomy for PIVD	Midazolam (0.05 mg/kg); Propofol (1.5–2.0 mg/kg); fentanyl (2.0 μg/kg); Vecuronium bromide (0.12 mg/kg), mixture of 50% air in oxygen and isoflurane (1%).	September 2014 to September 2016	A double blind placebo controlled study	Departm NA Anesthesiology, Sanjay Gandhi Post Graduate Institute of Medical Sciences; Lucknow
Sealing cuff pressure	/	/	60	Al-Metwalli (12)	8.35 ± 1.63 yr; 8.45 ± 1.76 yr; 8.2 ± 1.54 yr	Dental surgery	N2O free general anesthesia; 0.2 mg/kg oral diazepam; fentanyl 2 μg/kg and propofol 2.5 mg/kg.	NA	A prospective controlled, randomized, blinded study.	NA
Flexible laryngeal mask	/	/	90	Naguib (13)	3.24 ± 0.857 yr; 3.13 ± 0.815 yr	NA	Atropine 0.01 mg/kg; Fentanyl 1 μg/kg; Sevoflurane 3.5% in oxygen to air of 1:1	July 2018 to April 2019.	A randomized trial	Department of Pediatric Surgery, Tanta University Hospitals; Egypt

10.3389/fmed.2023.1289321

However, it is unfortunate that the type of disease the patient has is not well-defined in this article. Regarding hormonal prevention of post-extraction stridor, most of them are still focused on the patients in the intensive care unit, and only this study by Amoozadeh and Beigmohammadi suggests the effect of hormones before extubation in general anesthesia procedures (2). We made the following list of relevant postoperative extubation stridor after a literature search (Table 1).

In addition, we also noted that some of the differences in the induction and maintenance of anesthesia may also affect the extubation of patients, such as dexmedetomidine (11). Feng's et al. also pointed out that some of the data in the literature is missing and incomplete, and we believe that this part of the data is also often a relatively critical part of the data that affects the results, for example, the use of some sedative and antagonistic drugs (1). It is hoped that there will be a careful description of randomized controlled trials in the future, which will also help us to have a more comprehensive and accurate understanding of drug efficacy.

At the same time, we found two studies on extubation position and bloodletting acupuncture interesting, both of which showed that extubation in the lateral position may reduce the probability of postoperative dyspnea (3, 4, 8).

Author contributions

YS: Writing – original draft. HZ: Funding acquisition, Writing – review & editing. YM: Writing – original draft. YA: Funding acquisition, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The research received the grant from the Youth Science Fund Program of National Natural Science Foundation of China (NSFC) (No. 82202366).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Feng IJ, Lin J-W, Lai C-C, Cheng K-C, Chen C-M, Chao C-M, et al. Comparative efficacies of various corticosteroids for preventing postextubation stridor and reintubation: a systematic review and network meta-analysis. *Front Med.* (2023) 10:1135570. doi: 10.3389/fmed.2023.1135570

2. Amoozadeh L, Beigmohammadi MT. The effect of dexamethasone on the reduction of airway edema and the success of extubation in patients with head and neck surgery admitted to the intensive care unit. *Tehran Univ Med J.* (2022) 80:128–34. Available online at: https://www.embase.com/search/results?subaction=viewrecord&id=L2019206701&from=export

3. Xiang J-H, Wei P, Zhang Y-J, Li L-L, Li X, Wang J, et al. Safety of prone emergence from general endotracheal anesthesia in patients undergoing ERCP: a randomized controlled trial. *Surg Endosc.* (2023) 37:7493–501. doi: 10.1007/s00464-023-10187-7

4. Jung H, Kim HJ, Lee Y-C, Kim HJ. Comparison of lateral and supine positions for tracheal extubation in children : a randomized clinical trial. *Anaesthesist.* (2019) 68:303–8. doi: 10.1007/s00101-019-0590-2

5. Maddah SA, Barzegari A. The effect of albuterol spray on hypoxia and bronchospasm in patients with chronic obstructive pulmonary disease (COPD) under general anesthesia: a bouble-blind randomized clinical trial. *Ethiop J Health Sci.* (2023) 33:491–8. doi: 10.4314/ejhs.v33i3.12

6. Yang Q, Liu ZH, Chang YL. Clinical research on airway intervention before tracheal extubation after general anesthesia on snoring children. *Eur Rev Med Pharmacol Sci.* (2017) 21:109–13.

7. Weiss M, Dullenkopf A, Fischer JE, Keller C, Gerber AC, European Paediatric Endotracheal Intubation Study Group. Prospective randomized controlled multi-centre trial of cuffed or uncuffed endotracheal tubes in small children. *Br J Anaesth.* (2009) 103:867–73. doi: 10.1093/bja/aep290

8. Saghaei M, Razavi S. Bloodletting acupuncture for the prevention of stridor in children after tracheal extubation: a randomised, controlled study. *Anaesthesia.* (2001) 56:961–4. doi: 10.1046/j.1365-2044.2001.02228.x

9. Nishat M, Ahmad K, Tabassam S, Durrani NA, ul Haq U, ul Haqu F. Comparison of cuffed vs Uncuffed endotracheal intubation efficacy in cleft palate surgery procedure in children. *Pak J Med Health Sci.* (2021) 15:2379–81. doi: 10.53350/pjmhs211592379

10. Koç C, Kocaman F, Aygenç E, Ozdem C, Cekiç A. The use of preoperative lidocaine to prevent stridor and laryngospasm after tonsillectomy and adenoidectomy. *Otolaryngol Head Neck Surg.* (1998) 118:880–2. doi: 10.1016/S0194-5998(98)70290-6

11. Ambesh SP, Dubey M. Effect of intramuscular dexmedetomidine administration before extubation on post-extubation haemodynamics, postoperative sedation, and analgesic requirements: a double blind placebo controlled study. *Asian J Anesthesiol.* (2021) 59:102–10. doi: 10.6859/aja.202109_59(3).0004

12. Al-Metwalli RR, Sadek S. Safety and reliability of the sealing cuff pressure of the Microcuff pediatric tracheal tube for prevention of post-extubation morbidity in children: a comparative study. *Saudi J Anaesth.* (2014) 8:484–8. doi: 10.4103/1658-354X.140856

13. Naguib TM, Ahmed SA. Evaluation of flexible laryngeal mask airway(®) in tongue trauma repair: a randomized trial. *Anesth Pain Med.* (2019) 9:e92929. doi: 10.5812/aapm.92929

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 10 August 2023
DOI 10.3389/fmed.2023.1203023

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Yi Feng Wen,
Xi'an Jiaotong University, China
Habib Md Reazaul Karim,
All India Institute of Medical Sciences, Deoghar, India

*CORRESPONDENCE
Hong Jiang
✉ jianghong_jy@163.com
Ming Xia
✉ shxiaming1980@163.com

†These authors share first authorship

‡These authors have contributed equally to this work

RECEIVED 10 April 2023
ACCEPTED 31 July 2023
PUBLISHED 10 August 2023

CITATION
Pei B, Jin C, Cao S, Ji N, Xia M and Jiang H (2023) Geometric morphometrics and machine learning from three-dimensional facial scans for difficult mask ventilation prediction.
Front. Med. 10:1203023.
doi: 10.3389/fmed.2023.1203023

Geometric morphometrics and machine learning from three-dimensional facial scans for difficult mask ventilation prediction

Bei Pei†, Chenyu Jin†, Shuang Cao, Ningning Ji, Ming Xia*‡ and Hong Jiang*‡

Department of Anaesthesiology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Unanticipated difficult mask ventilation (DMV) is a potentially life-threatening event in anesthesia. Nevertheless, predicting DMV currently remains a challenge. This study aimed to verify whether three dimensional (3D) facial scans could predict DMV in patients scheduled for general anesthesia.

Methods: The 3D facial scans were taken on 669 adult patients scheduled for elective surgery under general anesthesia. Clinical variables currently used as predictors of DMV were also collected. The DMV was defined as the inability to provide adequate and stable ventilation. Spatially dense landmarks were digitized on 3D scans to describe sufficient details for facial features and then processed by 3D geometric morphometrics. Ten different machine learning (ML) algorithms, varying from simple to more advanced, were introduced. The performance of ML models for DMV prediction was compared with that of the DIFFMASK score. The area under the receiver operating characteristic curves (AUC) with its 95% confidence interval (95% CI) as well as the specificity and sensitivity were used to evaluate the predictive value of the model.

Results: The incidence of DMV was 35/669 (5.23%). The logistic regression (LR) model performed best among the 10 ML models. The AUC of the LR model was 0.825 (95% CI, 0.765–0.885). The sensitivity and specificity of the model were 0.829 (95% CI, 0.629–0.914) and 0.733 (95% CI, 0.532–0.819), respectively. The LR model demonstrated better predictive performance than the DIFFMASK score, which obtained an AUC of 0.785 (95% CI, 0.710–0.860) and a sensitivity of 0.686 (95% CI, 0.578–0.847). Notably, we identified a significant morphological difference in the mandibular region between the DMV group and the easy mask ventilation group.

Conclusion: Our study indicated a distinct morphological difference in the mandibular region between the DMV group and the easy mask ventilation group. 3D geometric morphometrics with ML could be a rapid, efficient, and non-invasive tool for DMV prediction to improve anesthesia safety.

KEYWORDS

difficult airway, difficult mask ventilation, predictive model, machine learning, three dimension scanning, geometric morphometrics

1. Introduction

Airway management is a critical aspect of ensuring the safety and quality of anesthesia. Mask ventilation (MV) is a cornerstone of airway management, serving as both an initial ventilation technique and a rescue method during difficult or failed tracheal intubation (1). Difficult mask ventilation (DMV) was reported to be an essential factor for severe airway-related complications such as death or hypoxic brain injury in anesthesia (2). As a result, it is essential to conduct a thorough assessment of the patient's airway before the induction of anesthesia. For patients with a high risk of DMV, the anesthesiologists can prepare alternative approaches in advance such as a plan for awake fiberoptic intubation to ensure safety (3).

Abnormal facial features can directly impact external mask fit, which potentially makes mask ventilation more challenging, and thus, the patient's morphology may be a relevant predictor for DMV. Recently, two-dimensional (2D) images and three-dimensional (3D) scans have been employed to characterize the maxillofacial structure and predict diseases (4, 5). In the field of anesthesia, 2D images have been implemented to construct a predictive model for the classification of difficult intubation (6, 7). However, 2D images are susceptible to external factors such as lighting, which may affect their accuracy. Moreover, human faces are inherently 3D objects, and 2D images are merely projections of the face on a flat surface, thus potentially resulting in a loss of important characteristics. To address these limitations, 3D scans are more suitable for examining the complex structures of facial shapes with greater reliability.

Conventional morphometric analysis that relies on linear measurements such as angles or lengths may not capture the complex variation in 3D shapes. Geometric morphometrics is a more effective tool as it can retain geometric information such as the relative position of each structure, allowing for quantification and visualization of morphometric results (8). For instance, the recent development in 3D craniofacial scans and geometric morphometric analysis has shown promising results in predicting obstructive sleep apnea (OSA), surpassing the performance of traditional questionnaires (9). It has been verified that there is a relationship between DMV and OSAS (10), and they share common morphological features, such as retrognathia and a thick neck.

No study has explored the relationship between 3D facial scans and DMV to our knowledge, so here we proposed that 3D geometric morphometric analysis of facial scans combined with machine learning (ML) algorithms could be an alternative tool to predict DMV in patients scheduled for general anesthesia.

2. Materials and methods

2.1. Patients

This observational study was conducted between June 2021 and January 2022 after obtaining approval from the Ethics Committee of Shanghai Ninth People's Hospital (no. SH9H-2020-T233-1). The protocol is registered on ClinicalTrials.gov (trial registration no. NCT 04458220). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The inclusion criteria for the study were adult patients scheduled for elective surgery under general anesthesia. The exclusion criteria were as follows: with mental or central nervous system disease; with stupefaction or disturbance of consciousness; with terrible injury; with difficulties in communicating; cannot follow instructions to make standardized postures; participated in other relevant clinical investigation in the past 3 months. Informed consent was provided by each participant before their inclusion.

2.2. Preoperative airway assessment

The demographic properties of patients' age, gender, weight, height, and body mass index (BMI) were collected during the preoperative visit. Drawing inspiration from a previous study that developed a weighted risk score for DMV prediction named DIFFMASK score (11), we collected additional data including the history of snoring, history of obstructive sleep apnea, history of neck radiation, history of difficult tracheal intubation, modified Mallampati test (MMT), and thyromental distance (TMD).

All researchers received repeated training before this trial to reduce measurement bias. The modified Mallampati test (MMT) was conducted with patients in full neck extension, while being asked to open their mouths widely and protrude their tongues, without vocalizing (12). The thyromental distance was determined by measuring the distance between the uppermost border of the thyroid cartilage and the mentum, with the neck in an extended position (12).

2.3. 3D geometric morphometrics of the craniofacial structure

2.3.1. Facial surface imaging

All 3D scans were acquired in the Shanghai Ninth People's Hospital by the same researcher who was specifically trained prior to the trial to ensure the uniformity of data.

A 3D face scanner, FaceGo pro (Revopoint, China) was utilized to generate 3D facial models with an accuracy of 0.1 mm. Participants were instructed to fully expose their face and neck region, maintain a neutral facial expression, and look parallelly at the camera during the scanning process, with their heads in a natural position. Each participant was asked to keep the head still during the whole scan which could be finished in 1 min.

2.3.2. Manual annotation

The models were saved in OBJ format and subsequently processed using Meshmixer (release 3.5.474)[1] to eliminate the redundant parts. Each facial scan in OBJ format was imported into the 3D Slicer (release 5.0.3)[2] which is an open-source biomedical visualization and image analysis software supported by the National Institutes of Health (NIH) (13) to digitize 8 anchoring points (pronasale, right earlobe, left earlobe, right cheilion, left cheilion, tip of the chin, hyoid bone, and thyroid notch) in a fixed order (Figures 1A,B). The placement of anchoring points was performed by a single researcher to minimize potential user bias.

1 https://meshmixer.com/

2 https://www.slicer.org/

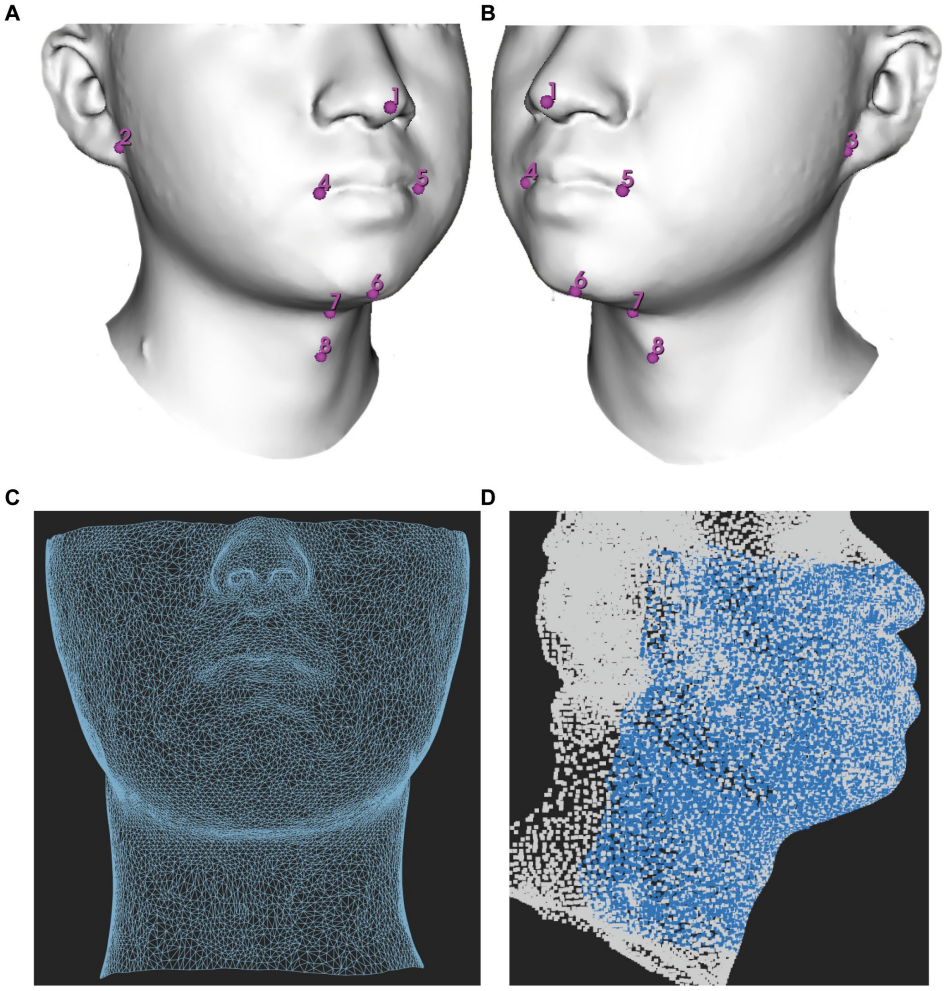


FIGURE 1
Demonstration of facial mapping. **(A)** Digitization of eight anchoring points on a 3D model in a right lateral view. **(B)** Digitization of eight anchoring points on a 3D model in a right left view. **(C)** The reference mesh, consisting of 9,578 vertices and 18,812 faces formed by three adjacent vertices, was illustrated as a wireframe model. **(D)** Spatially dense facial landmarks (blue) were mapped onto reference mesh shown in a lateral view illustrated as a point cloud model.

2.3.3. Spatially dense surface registration

All acquisitions were mapped using MeshMonk, an open-source software toolbox available at https://github.com/TheWebMonks/meshmonk, within MATLAB 2018b. MeshMonk facilitates spatially dense registration of 3D surfaces (14). Through iterative rigid and non-rigid registration algorithms, MeshMonk enables the alignment of each 3D surface to a reference mesh.

A single patient with a fully exposed head and neck region and minimal caveats was selected as the reference mesh. The choice of reference mesh has little impact on statistics, as long as it fulfills the criteria of having no significant holes and uniform vertex coverage (15).

The reference mesh was subsequently cleaned and prepared using Meshmixer (version 3.5.474), accessible at https://meshmixer.com/. The cleanup process aimed to retain the area below the eyes and above the plane of the thyroid cartilage, as it held significant interest for DMV shown in Figure 1C. Our hypothesis was that this region, from below the eyes to above the jaw, could affect mask ventilation by influencing mask fit while the region of mandible and neck could potentially interfere with mask ventilation by impacting airflow. Following the cleanup, the reference mesh consisted of 9,578 vertices. The reference mesh in OBJ format could be found in Supplementary file.

Subsequently, the reference mesh underwent iterative rigid and non-rigid registration algorithms to align each facial image. As the same reference mesh was used, the landmarks redefined on each facial sample were matched point-to-point consistently across all samples (16).

To explore the potential impact of using different reference meshes from different patients, we randomly selected three additional patients. Subsequently, each facial image was aligned to different reference mesh for subsequent analyses.

2.3.4. Generalized procrustes analysis

A Generalized Procrustes analysis (GPA) was then applied to re-align all meshes into a common coordinate system, using a total of 9,578 quasi-landmarks which removed among configuration variations in size, location, and orientation (17).

2.4. Dimensionality reduction

A total of 9,578 quasi-landmarks were available to characterize each patient's maxillofacial and neck shape. A principal component analysis (PCA) was then applied to the Procrustes-aligned coordinates to reduce the dimensionality of the data and extract a smaller set of orthogonal dimensions that captured the variability in the dataset. A linear discriminant analysis (LDA) was employed using a simple Leave-One-Out Cross-Validation (LOOCV) technique systematically increasing the number of principal components (PCs) from 1 to 50 as input to determine the optimal number of PCs for predicting DMV. In LOOCV, one sample was used as the validation data, while the rest were used as the training data. This process was repeated such that each sample in the dataset was used once as the validation data. The optimal number of PCs for predicting DMV was determined based on the highest value of the area under the receiver operating characteristic curve (AUC).

The morphometric data was processed by the R project software program (R 4.2.2)[3] mainly using geomorph (18) and Morpho packages (19). The LDA used MASS packages and the self-generated code was developed to implement LOOCV.

2.5. Induction of anesthesia and MV evaluation

Airway management was conducted by an anesthesiologist with over 3 years of experience. General anesthesia was induced with a combination of midazolam 0.05 mg/kg, fentanyl 2–4 μg/kg, propofol 2–2.5 mg/kg, and rocuronium 0.6 mg/kg. The patient's head was placed in the 'sniffing position' by extending the neck and throughout the procedure, electrocardiography, noninvasive blood pressure, end-tidal carbon dioxide, and peripheral oxygen saturation (SpO_2) were continuously monitored.

During the induction of anesthesia, the anesthesiologist was instructed to employ a one-handed technique for airway opening. This involved holding the anesthesia full-face mask (Flexicare, United Kingdom; sizes 3 and 4) with their thumb and index fingers while positioning the third and fourth fingers on the left mandibular ramus, and placing the fifth finger at the left mandibular angle.

Following the induction of anesthesia, pressure-controlled ventilation was initiated through the full-face mask *via* an anesthesia machine ventilator, with a peak inspiratory pressure of 15 cm H_2O, positive end-expiratory pressure of 0, I: E ratio of 0.4, and a respiratory rate of 15 cycles per minute for a duration of 2 min.

During face mask ventilation, one-handed technique without adjuvant (such as oral airway and jaw thrust) by an unassisted anesthesiologist was routinely utilized. DMV was defined as the inability to achieve adequate ventilation using this technique. The inadequate ventilation was defined according to Langeron et al. (20) as follows: (1) the inability of an unassisted anesthesiologist to maintain oxygen saturation, as measured by $SpO_2 < 92\%$ with 100% oxygen and positive-pressure mask ventilation; (2) important gas flow leakage around the face mask; (3) the need to increase the gas flow to more than 15 L/min and use the oxygen flush valve more than twice (4) absence of visible chest movement; (5) the necessity to switch to a two-handed mask ventilation technique; (6) the need for operator substitution.

In clinical practice, we observed that the perceptible chest movement was subjective so we also considered ventilation inadequate if the tidal volume was less than 5 mL/kg ideal body weight, following the study by Sato et al. (10).

To ensure the safety of patients if inadequate ventilation was encountered, steps were taken to address the situation effectively as recommended by the guidelines (21). This involved inserting an appropriately sized oral airway and applying an optimal jaw thrust technique while securely holding the mask with both hands. If these measures were unsuccessful, seeking help, changing the operator, or involving a two-person technique was considered. If adequate ventilation cannot be achieved, careful consideration is given to either waking patients using sugammadex to reverse the neuromuscular blockade induced by rocuronium or promptly establishing a noninvasive artificial airway, such as a supraglottic airway or endotracheal intubation. If these interventions also fail, cricothyrotomy should be performed immediately.

2.6. Machine learning algorithms

For the purpose of building a prediction model, a total of 10 ML algorithms, including Naive Bayes, linear discriminant analyses (LDA), quadratic discriminant analysis (QDA), logistic regression (LR), support vector machine (SVM), random forest (RF), extra trees, artificial neural network (ANN), adaptive boosting (AdaBoost), and extreme gradient boosting (XGBoost), representing diverse categories were performed using the morphometric data (22). Each algorithm has its own advantages and disadvantages, and our aim was to identify the most appropriate algorithm for our data. The model's performance was assessed using the 10-fold cross-validation method (23). This approach involved dividing the cohort into ten folds. In each iteration of the cross-validation process, one fold was set aside for evaluation purposes, while the remaining nine folds were utilized for training the model. By iteratively changing the validation fold in each round of the cross-validation process, each part of the cohort served as the validation set exactly once. This process enhanced the robustness of the evaluation and contributed to a more reliable assessment of the model's performance.

2.7. Statistical analysis

The measurement data were presented as mean ± standard deviation (SD), whereas categorical variables were expressed as frequency (%). The hypothesis was tested using one-way analysis of variance (ANOVA), the Mann–Whitney U test, and Fisher's exact probability method. Statistical significance was defined as $p < 0.05$. To assess classification performance, the area under the receiver operating characteristic curve (AUC) with its 95% confidence interval (95% CI), as well as the sensitivity and specificity, were utilized as primary metrics. All data analysis was conducted utilizing the R project software program (R 4.2.2) (see footnote 3).

3 https://cran.r-project.org/bin/windows/base/

TABLE 1 The baseline demographic properties and risk factors for patients included.

Risk factors	Overall (n = 669)	Easy MV (n = 634)	DMV (n = 35)	p value
Age (years)	34.67 ± 11.53	34.32 ±11.38	40.94 ±12.61	0.001
Gender				<0.001
Female	375 (56.1)	366 (57.7)	9 (25.7)	
Male	294 (43.9)	268 (42.3)	26 (74.3)	
BMI (kg/m^2)	22.18 ± 3.41	21.90 ± 3.16	27.30 ± 3.64	<0.001
TMD (cm)	9.52 ± 1.35	9.50 ± 1.36	9.76 ± 1.13	0.269
Snoring history				<0.001
Yes	282 (42.2)	256 (40.4)	26 (74.3)	
No	387 (57.8)	378 (59.6)	9 (25.7)	
Neck radiation history				0.044
Yes	1 (0.1)	0 (0)	1 (2.9)	
No	668 (99.9)	634 (100.0)	34 (97.1)	
DI history				0.044
Yes	1 (0.1)	0 (0)	1 (2.9)	
No	668 (99.9)	634 (100.0)	34 (97.1)	
Sleep apnea				1.000
Yes	1 (0.1)	1 (0.2)	0 (0)	
No	668 (99.9)	633 (99.8)	35 (100.0)	
MMT				0.735
1	152 (22.7)	145 (22.9)	7 (20.0)	
2	223 (33.3)	212 (33.4)	11 (31.4)	
3	262 (39.2)	248 (39.1)	14 (40.0)	
4	32 (4.8)	29 (4.6)	3 (8.6)	

Data are shown as number (percentage) or mean ± SD; SD, standard deviation; MV, mask ventilation; DMV, difficult mask ventilation; BMI, body mass index; TMD, thyromental distance; DI, difficult intubation; MMT, modified Mallampati test.

We used the method by Riley et al. to calculate for the efficient sample size (24). We did not calculate the sample size in advance because we utilized all accessible data throughout the study period. However, we did a *post hoc* sample size calculation to verify whether the developed models ensure accurate prediction. In our study, selecting an estimated C statistic of 0.825, a prevalence of DMV 5.23%, and a predictor parameters of 3, model development required at least 331 cases. Our total sample size included 669 patients which satisfied the minimum sample size requirement.

3. Results

3.1. Baseline characteristics

A total of 734 patients initially screened. Thirty-eight patients were excluded because of the poor quality of 3D scans. Twenty-five patients were excluded because of postponed surgery, and 2 patients were excluded because they underwent awake intubation. Finally, 669 patients were enrolled, including 634 patients with easy MV and 35 patients with DMV. A flow chart of the study is shown in Figure 2. The baseline characteristics of the study population are presented in Table 1. Statistical analysis revealed significant differences in age, gender, BMI, and snoring history between the DMV group and the easy MV group. Only a single patient in the DMV group had a history of neck radiation and difficult intubation. None of the patients received sugammadex or rescue ventilation devices.

3.2. The principal component analysis

Principal component analysis (PCA) demonstrated that the first three principal components (PCs) were responsible for describing 42.63% of the total variance in the data. 75% of the total variance can be described only by 14 PCs. The LDA was performed using a range of a range of PCs from 1 to 50 as input, with a LOOCV technique. The results showed that the highest AUC of 0.819 (95% CI, 0.758–0.880) was achieved when only the first 3 PCs were processed, with a sensitivity of 0.829 (95% CI, 0.657–0.943) and a specificity of 0.700 (95% CI, 0.513–0.765) when the highest point of the Youden index was the threshold.

After that, there was a brief decline in the performance of the model as the number of PCs increased, and then there was some improvement when with the first 14 PCs as input, but it still did not exceed the performance of using the first 3 PCs and after that the performance of the model continued decline as the number of PCs increased (Figure 3). This is the cost of dimensionality based on morphometric data in classification.

Using scans from 3 random participants as the reference mesh, realigned them with all patients' scans, had a negligible effect on the performance of the models (Supplementary Table S1).

3.3. DMV prediction from morphometric data

Based on the preliminary test results, we observed two peaks in the first 2 to 5 PCs and the first 13 to 15 PCs. Consequently, we chose to explore the first 2 to 5 PCs and 13 to first 13 to 15 PCs to further investigate the optimal number of PCs and identify the best algorithm for our analysis. The predictive performance was evaluated using the 10-fold cross-validation method (Table 2). The SVM, extra trees, and AdaBoost showed relatively poor performance. However, the other algorithms exhibited good predictive performance, with AUC over 0.80. At this step, the LR model was selected as the preferred algorithm due to its speed and superior performance. When only 3 PCs were input, this model achieved an AUC of 0.825 (95% CI, 0.765–0.885) by the 10-fold cross-validation method with a sensitivity of 0.829 (95% CI, 0.629–0.914), and a specificity of 0.733 (95% CI, 0.532–0.819) (Figure 4).

3.4. Comparison to DIFFMASK score

The DIFFMASK score got an AUC of 0.785 (95% CI, 0.710–0.860). The Youden index identified a score ≥ 4 as the optimal cut-off value for DMV prediction, with a sensitivity of 0.686 (95% CI,

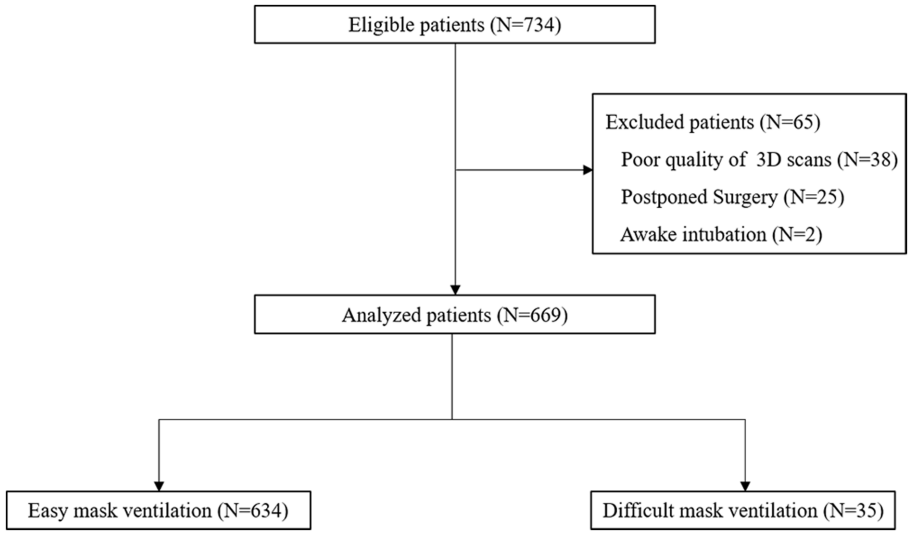


FIGURE 2
Flow chart of the study.

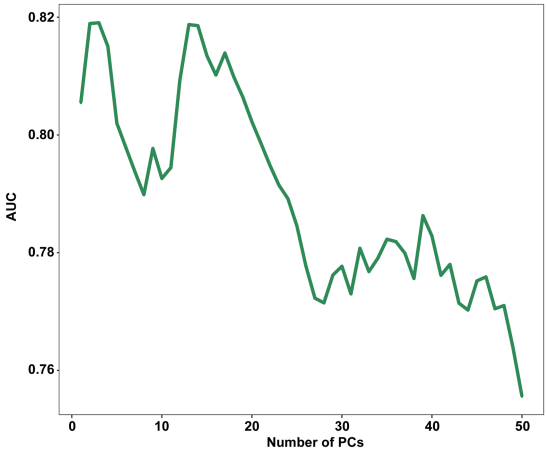


FIGURE 3
Influence of the number of PCs retained on the AUC score. PC, principal component; AUC, The area under the receiver operating characteristic curves.

0.578–0.847) and a specificity of 0.785 (95% CI, 0.589–0.848). The performance of the morphometric data surpassed those of the DIFFMASK scores.

3.5. Visual prediction of DMV

The average shape was computed based on all the sample shape vectors in the DMV group and easy MV group (Figures 5A,B). The differences in shape between the DMV group and the easy MV group was shown in Figure 5C. The most obvious difference between the two groups could be observed in the mandibular region.

4. Discussion

This study aimed to demonstrate the association between maxillofacial geometry and the risk of DMV while developing a prediction model for DMV with morphometric data and ML algorithms. Our study suggested that using only the first 3 PCs as inputs, with the LR algorithm allowed for effective DMV prediction, achieving an AUC of 0.825 (95% CI, 0.765–0.885), which outperformed the DIFFMASK score.

During the preliminary test, the model exhibited its best performance with only the first 3 PCs. However, as the number of PCs increased, the overall trend was a decline in performance. This suggests that the first 3 PCs were sufficient in capturing the essential characteristics of the 3D morphological data. After 14 PCs, the performance of the model continued to decline which can be attributed to the curse of dimensionality commonly seen in morphometric data-based classification tasks (25). The later PCs might capture noise rather than meaningful information, thereby increasing data complexity and necessitating larger sample sizes.

Based on the results obtained from the preliminary test, when modeling with the first 2–5 PCs and the first 13–15 PCs, the best-performing model among the 10 ML algorithms tested was achieved by using the first 3 PCs with LR. LR is commonly employed as a modeling approach for binary outcomes in epidemiology and medicine (26). Despite the growing popularity of more complex ML algorithms, LR consistently demonstrated comparable performance and, in some cases, can even outperform these complex ML algorithms (27, 28). Across different ML algorithms in clinical risk prediction, there was considerable variability, whereas LR was generally regarded as stable (29). Complex ML algorithms such as ANN and SVM have the advantage in capturing nonlinear relationships in the data, but our data might not have exhibited strong nonlinear patterns. Furthermore, complex ML algorithms are most suitable for medical prediction

TABLE 2 The AUC (95% CI) of the models evaluated by 10-fold cross-validation using various machine learning algorithms with 2 to 5 PCs and 13 to 15 PCs inputs.

Variables	2 PCs (95% CI)	3 PCs (95% CI)	4 PCs (95% CI)	5 PCs (95% CI)	…	13 PCs (95% CI)	14 PCs (95% CI)	15 PCs (95% CI)
Naive Bayes	0.818 (0.754–0.881)	0.810 (0.746–0.872)	0.798 (0.731–0.865)	0.786 (0.713–0.860)	…	0.775 (0.702–0.847)	0.774 (0.702–0.846)	0.768 (0.696–0.841)
LDA	0.820 (0.759–0.882)	0.823 (0.764–0.882)	0.818 (0.758–0.877)	0.799 (0.728–0.870)	…	0.815 (0.746–0.884)	0.814 (0.746–0.882)	0.810 (0.740–0.881)
QDA	0.812 (0.747–0.878)	0.797 (0.728–0.867)	0.778 (0.707–0.850)	0.774 (0.698–0.851)	…	0.718 (0.627–0.809)	0.757 (0.672–0.843)	0.746 (0.665–0.826)
LR	0.823 (0.762–0.884)	0.825 (0.765–0.885)	0.820 (0.760–0.880)	0.805 (0.737–0.872)	…	0.818 (0.753–0.883)	0.818 (0.755–0.881)	0.815 (0.749–0.881)
SVM	0.560 (0.470–0.650)	0.608 (0.500–0.716)	0.569 (0.474–0.664)	0.546 (0.452–0.639)	…	0.706 (0.623–0.790)	0.645 (0.560–0.730)	0.678 (0.587–0.770)
RF	0.765 (0.683–0.846)	0.758 (0.678–0.837)	0.810 (0.733–0.887)	0.799 (0.717–0.881)	…	0.758 (0.667–0.849)	0.759 (0.664–0.855)	0.773 (0.685–0.862)
Extra trees	0.673 (0.579–0.766)	0.612 (0.514–0.711)	0.618 (0.521–0.715)	0.614 (0.521–0.708)	…	0.691 (0.602–0.781)	0.681 (0.587–0.774)	0.681 (0.587–0.774)
ANN	0.778 (0.700–0.856)	0.810 (0.741–0.877)	0.794 (0.720–0.868)	0.782 (0.701–0.862)	…	0.805 (0.732–0.878)	0.761 (0.684–0.839)	0.773 (0.695–0.852)
AdaBoost	0.726 (0.630–0.823)	0.686 (0.598–0.774)	0.759 (0.668–0.851)	0.761 (0.671–0.851)	…	0.761 (0.677–0.846)	0.725 (0.623–0.827)	0.732 (0.634–0.831)
XGBOOST	0.788 (0.700–0.876)	0.803 (0.725–0.881)	0.797 (0.718–0.875)	0.781 (0.694–0.868)	…	0.809 (0.732–0.886)	0.807 (0.729–0.885)	0.808 (0.730–0.886)

AUC, the area under the receiver operating characteristic curves; CI, confidence interval; PCs, principal components; LDA, linear discriminant analyses; QDA, quadratic discriminant analysis; LR, logistic regression; SVM, support vector machine; RF, random forest; ANN, artificial neural network; AdaBoost, adaptative boosting; XGBOOST, eXtreme Gradient Boosting.

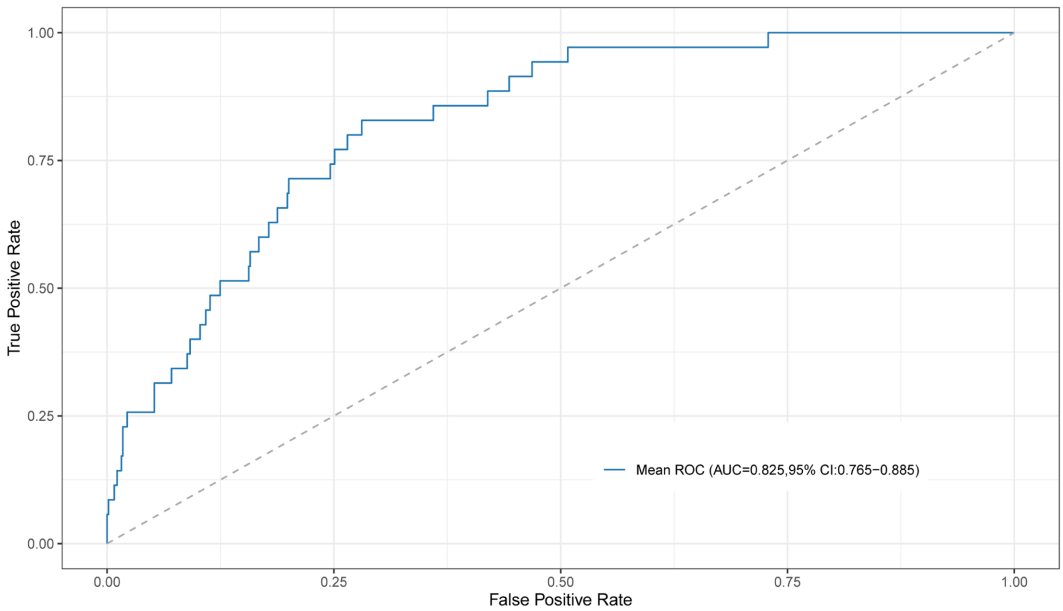


FIGURE 4
The ROC curve for the LR model with 10-fold cross-validation using the first 3 PCs as input. ROC, receiver operating characteristic; PC, principal component.

problems with large datasets, whereas LR modeling requires less data and is particularly advantageous when working with relatively small datasets (30).

The human face contains a wealth of pathophysiological information, numerous studies have investigated the relationship between facial images and diseases such as coronary artery disease

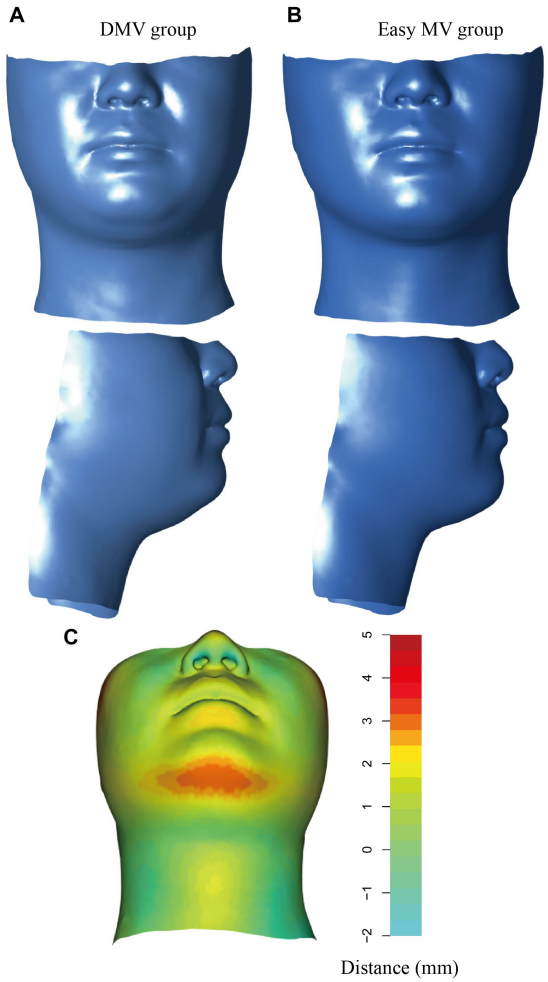


FIGURE 5
Visualization of the DMV group and the easy MV group. **(A)** Mean shape for the DMV group. **(B)** Mean shape for the easy MV group. **(C)** Colors represent the distances from the mean shape of the DMV group and the mean shape of the easy MV group. DMV, difficult mask ventilation; MV, mask ventilation.

(31) and acromegaly (32). In the field of anesthesia, facial images have been developed to classify intubation difficulty which showed a good performance with an AUC of 0.864 (6). Although 2D image acquisition is straightforward, it is more susceptible to variations such as camera angle, focal depth, and lighting. Counterintuitively, 2D images are more complicated than 3D meshes due to their high dimensional and intricate color image variation that is nonlinear. Consequently, processing 2D data requires the use of large, complex, nonlinear network architectures and substantial training datasets. Conversely, the distribution of 3D meshes can be efficiently approximated by multivariate Gaussian distributions and analyzed using geometric morphometrics (33). With the development of 3D devices, the potential of 3D scans for predicting disease has been validated. For example, 3D facial morphology has been introduced in the discrimination of genetic syndromes such as 22q11 deletion syndromes and fetal alcohol syndrome (34, 35). More recently, 3D craniofacial scans have been developed to build the prediction model of OSAS with an AUC of 0.70 and a sensitivity of 74% (9).

Our study exemplified the application of 3D scans to DMV predicition. Mask ventilation is a fundamental technique used in general anesthesia. Currently, the prediction of DMV relies mainly on patient history and traditional bedside examinations (36). A prospective study of 1,502 patients identified five risk factors to be significantly associated with DMV including age > 55 years, BMI > 26 kg/m^2, lack of teeth, history of snoring, and presence of a beard (20). Similarly, our study found that age, BMI and history of snoring showed significant differences among DMV and easy MV group. However, the diagnostic accuracy of DMV prediction based on these factors has been proven to be poor, with up to 94% of DMV patients ultimately failing to be predicted (37). For this reason, the DIFFMASK score (which incorporated age, sex, BMI, history of difficult intubation, history of snoring, thyromental distance, Modified Mallampati test, beard, sleep apnea, and history of neck radiation) ranging from 0 to 18 points was developed and validated in a large cohort of 46,804 patients (11). Patients with a sum score ≥ 5 were deemed to be at risk for DMV. Our study validated the predictive value of this score, with an AUC of 0.785, and different from the previous study, the optimal cut-off value was 4. This might be attributed to the absence of patients with a beard and relatively few patients with a history of neck radiation and sleep apnea. In our study, the LR model with morphometric data outperformed the DIFFMASK score. This may potentially be explained by the extensive range of information carried by facial morphology, including age (38), gender (39), and most notably, the distribution of soft tissue across the region of the face and neck, which cannot be described through BMI.

We computed the average shapes of the DMV group and easy MV group, it was apparent that the DMV group exhibited excessive soft tissue in the mandibular region, which potentially altered compliance of the upper airway wall and narrowed the upper airway lumen, resulting in airway collapse during anesthesia.

To our knowledge, no prior studies have explored the relationship between facial anatomy and DMV. However, several studies have identified specific craniofacial features in patients with difficult intubation (DI). There was a relationship between DMV and the incidence of DI. The past study verified that patients with DMV experienced a higher incidence of DI compared to those with easy MV (20). A study conducted among Japanese reported that patients who had difficulty with intubation had an increased submandible angle, which is formed by the intersection of the line between the tragus and the mentum with the submandible line (40). Another study conducted on 80 Caucasian males revealed that individuals with DI had a significantly greater jaw-neck slope compared to those with easy intubation (41). Similarly, our study confirmed that patients with DMV had such maxillofacial structures. These morphological differences can partially explain the association between DMV and DI.

The incidence of DMV varies among reported studies, possibly due to the absence of standard criteria for its definition. The ASA Task Force's definition was subjective and vague (42) while Han et al.'s was considered too stringent and potentially led to an underestimation of DMV incidence (43). Therefore, the definition by Langeron et al. (20) was utilized in this study. It is important to note that different definitions of DMV may result in variations in incidence and can potentially impact the performance of predictive models.

There were still some limitations in this study. Firstly, the sample was limited to Chinese Han adults and may not be generalizable to other ethnic groups or younger populations. Given that facial morphology differs across races and age groups, further investigations including diverse populations are warranted to determine the association between facial features and DMV. Secondly, the study

exclusively focused on patients scheduled for elective surgery who were able to undergo a 3D scan while awake and cooperative. Consequently, the model developed may not be applicable to critically ill patients or emergency surgical scenarios. Lastly, it is important to note that further research is needed to validate the prediction model's performance on various 3D scanning devices, including handheld ones, to support its use in clinical practice.

In conclusion, this was the first study to use 3D facial scans combined with a machine learning algorithm (here is LR) to build the prediction model for DMV which achieved a good performance. The visualization demonstrated the shape differences between DMV and the easy MV group. This non-invasive and convenient approach has promising applications for DMV prediction. Nevertheless, further studies are required to validate the generalizability and clinical utility of this novel tool on a larger scale.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Shanghai Ninth People's Hospital (no. SH9H-2020-T233-1). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MX and HJ contributed to the conception of the study. BP, CJ, SC, and MX contributed to the methodology of the study. BP and CJ contributed to the collection and assembly of data. BP and NJ contributed to the data analysis and interpretation. BP, CJ, MX, and HJ contributed to the writing, review, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Clinical Research Program of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (no. JYLJ202013).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1203023/full#supplementary-material

References

1. El-Orbany M, Woehlck HJ. Difficult mask ventilation. *Anesth Analg*. (2009) 109:1870–80. doi: 10.1213/ANE.0b013e3181b5881c

2. Cook TM, Woodall N, Frerk C. Major complications of airway management in the UK: results of the fourth National Audit Project of the Royal College of anaesthetists and the difficult airway society. Part 1: anaesthesia. *Br J Anaesth*. (2011) 106:617–31. doi: 10.1093/bja/aer058

3. Cook TM, MacDougall-Davis SR. Complications and failure of airway management. *Br J Anaesth*. (2012) 109:i68–85. doi: 10.1093/bja/aes393

4. Schwab RJ, Leinwand SE, Bearn CB, Maislin G, Rao RB, Nagaraja A, et al. Digital morphometrics: a new upper airway phenotyping paradigm in OSA. *Chest*. (2017) 152:330–42. doi: 10.1016/j.chest.2017.05.005

5. Lin SW, Sutherland K, Liao YF, Cistulli PA, Chuang LP, Chou YT, et al. Three-dimensional photography for the evaluation of facial profiles in obstructive sleep apnoea. *Respirology*. (2018) 23:618–25. doi: 10.1111/resp.13261

6. Hayasaka T, Kawano K, Kurihara K, Suzuki H, Nakane M, Kawamae K. Creation of an artificial intelligence model for intubation difficulty classification by deep learning (convolutional neural network) using face images: an observational study. *J Intensive Care*. (2021) 9:38. doi: 10.1186/s40560-021-00551-x

7. Cuendet GL, Schoettker P, Yüce A, Sorci M, Gao H, Perruchoud C, et al. Facial image analysis for fully automatic prediction of difficult endotracheal intubation. *IEEE Trans Biomed Eng*. (2016) 63:328–39. doi: 10.1109/tbme.2015.2457032

8. Katsube M, Yamada S, Utsunomiya N, Morimoto N. Application of geometric morphometrics for facial congenital anomaly studies. *Congenit Anom (Kyoto)*. (2022) 62:88–95. doi: 10.1111/cga.12461

9. Monna F, Ben Messaoud R, Navarro N, Baillieul S, Sanchez L, Loiodice C, et al. Machine learning and geometric morphometrics to predict obstructive sleep apnea from 3D craniofacial scans. *Sleep Med*. (2022) 95:76–83. doi: 10.1016/j.sleep.2022.04.019

10. Sato S, Hasegawa M, Okuyama M, Okazaki J, Kitamura Y, Sato Y, et al. Mask ventilation during induction of general Anesthesia: influences of obstructive sleep Apnea. *Anesthesiology*. (2017) 126:28–38. doi: 10.1097/aln.0000000000001407

11. Lundstrøm LH, Rosenstock CV, Wetterslev J, Nørskov AK. The DIFFMASK score for predicting difficult facemask ventilation: a cohort study of 46,804 patients. *Anaesthesia*. (2019) 74:1267–76. doi: 10.1111/anae.14701

12. Detsky ME, Jivraj N, Adhikari NK, Friedrich JO, Pinto R, Simel DL, et al. Will this patient be difficult to intubate?: the rational clinical examination systematic review. *JAMA*. (2019) 321:493–503. doi: 10.1001/jama.2018.21413

13. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D slicer as an image computing platform for the quantitative imaging network. *Magn Reson Imaging*. (2012) 30:1323–41. doi: 10.1016/j.mri.2012.05.001

14. White JD, Ortega-Castrillón A, Matthews H, Zaidi AA, Ekrami O, Snyders J, et al. MeshMonk: open-source large-scale intensive 3D phenotyping. *Sci Rep*. (2019) 9:6085. doi: 10.1038/s41598-019-42533-y

15. Hutton TJ, Buxton B, Hammond P. Dense surface point distribution models of the human face. Proceedings IEEE Workshop on Mathematical Methods in Biomedical Image Analysis (MMBIA 2001); IEEE (2001) 153–160.

16. Chen W, Qian W, Wu G, Chen W, Xian B, Chen X, et al. Three-dimensional human facial morphologies as robust aging markers. *Cell Res*. (2015) 25:574–87. doi: 10.1038/cr.2015.36

17. Rohlf FJ, Slice DJ. Extensions of the procrustes method for the optimal superimposition of landmarks. *Syst Biol*. (1990) 39:40–59. doi: 10.2307/2992207

18. Adams DC, Otárola-Castillo E. Geomorph: anrpackage for the collection and analysis of geometric morphometric shape data. *Methods Ecol Evol*. (2013) 4:393–9. doi: 10.1111/2041-210X.12035

19. Schlager S. Morpho and Rvcg–Shape Analysis in R: R-Packages for geometric morphometrics, shape analysis and surface manipulations[M]//Statistical shape and deformation analysis. Academic Press (2017) 217–256.

20. Langeron O, Masso E, Huraux C, Guggiari M, Bianchi A, Coriat P, et al. Prediction of difficult mask ventilation. *Anesthesiology*. (2000) 92:1229–36. doi: 10.1097/00000542-200005000-00009

21. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult airway society 2015 guidelines for management of unanticipated difficult intubation in adults. *Br J Anaesth*. (2015) 115:827–48. doi: 10.1093/bja/aev371

22. Singh A, Thakur N, Sharma A. A review of supervised machine learning algorithms. 2016 3rd International Conference on Computing for Sustainable Global Development (INDIACom) Piscataway: IEEE (2016) 1310–5.

23. Krstajic D, Buturovic LJ, Leahy DE, Thomas S. Cross-validation pitfalls when selecting and assessing regression and classification models. *J Cheminform*. (2014) 6:10. doi: 10.1186/1758-2946-6-10

24. Riley RD, Ensor J, Snell KIE, Harrell FE Jr, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. (2020) 368:m441. doi: 10.1136/bmj.m441

25. Köppen M. "The Curse of Dimensionality" in 5th Online World Conference on Soft Computing in Industrial Applications (WSC5). (2000) 1:4–8.

26. Kleinbaum DG, Klein M. Introduction to logistic regression. in *Logistic Regression: A Self-Learning Text*. eds. Kleinbaum DG, Klein M. (New York, NY: Springer). (2010) 1–39.

27. Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol*. (2019) 110:12–22. doi: 10.1016/j.jclinepi.2019.02.004

28. Nusinovici S, Tham YC, Chak Yan MY, Wei Ting DS, Li J, Sabanayagam C, et al. Logistic regression was as good as machine learning for predicting major chronic diseases. *J Clin Epidemiol*. (2020) 122:56–69. doi: 10.1016/j.jclinepi.2020.03.002

29. Song X, Liu X, Liu F, Wang C. Comparison of machine learning and logistic regression models in predicting acute kidney injury: a systematic review and meta-analysis. *Int J Med Inform*. (2021) 151:104484. doi: 10.1016/j.ijmedinf.2021.104484

30. van der Ploeg T, Austin PC, Steyerberg EW. Modern modelling techniques are data hungry: a simulation study for predicting dichotomous endpoints. *BMC Med Res Methodol*. (2014) 14:137. doi: 10.1186/1471-2288-14-137

31. Lin S, Li Z, Fu B, Chen S, Li X, Wang Y, et al. Feasibility of using deep learning to detect coronary artery disease based on facial photo. *Eur Heart J*. (2020) 41:4400–11. doi: 10.1093/eurheartj/ehaa640

32. Kizilgul M, Karakis R, Dogan N, Bostan H, Yapici MM, Gul U, et al. Real-time detection of acromegaly from facial images with artificial intelligence. *Eur J Endocrinol*. (2023) 188:158–65. doi: 10.1093/ejendo/lvad005

33. Hallgrímsson B, Aponte JD, Katz DC, Bannister JJ, Riccardi SL, Mahasuwan N, et al. Automated syndrome diagnosis by three-dimensional facial imaging. *Genet Med*. (2020) 22:1682–93. doi: 10.1038/s41436-020-0845-y

34. Hammond P, Hutton TJ, Allanson JE, Buxton B, Campbell LE, Clayton-Smith J, et al. Discriminating power of localized three-dimensional facial morphology. *Am J Hum Genet*. (2005) 77:999–1010. doi: 10.1086/498396

35. Fang S, McLaughlin J, Fang J, Huang J, Autti-Rämö I, Fagerlund A, et al. Automated diagnosis of fetal alcohol syndrome using 3D facial image analysis. *Orthod Craniofac Res*. (2008) 11:162–71. doi: 10.1111/j.1601-6343.2008.00425.x

36. Nørskov AK, Wetterslev J, Rosenstock CV, Afshari A, Astrup G, Jakobsen JC, et al. Prediction of difficult mask ventilation using a systematic assessment of risk factors vs. existing practice – a cluster randomised clinical trial in 94,006 patients. *Anaesthesia*. (2017) 72:296–308. doi: 10.1111/anae.13701

37. Nørskov AK, Rosenstock CV, Wetterslev J, Astrup G, Afshari A, Lundstrøm LH. Diagnostic accuracy of anaesthesiologists' prediction of difficult airway management in daily clinical practice: a cohort study of 188 064 patients registered in the Danish anaesthesia database. *Anaesthesia*. (2015) 70:272–81. doi: 10.1111/anae.12955

38. Xia X, Chen X, Wu G, Li F, Wang Y, Chen Y, et al. Three-dimensional facial-image analysis to predict heterogeneity of the human ageing rate and the impact of lifestyle. *Nat Metab*. (2020) 2:946–57. doi: 10.1038/s42255-020-00270-x

39. Wu J, Smith WAP, Hancock ER. Facial gender classification using shape-from-shading. *Image Vis Comput*. (2010) 28:1039–48. doi: 10.1016/j.imavis.2009.09.003

40. Suzuki N, Isono S, Ishikawa T, Kitamura Y, Takai Y, Nishino T. Submandible angle in nonobese patients with difficult tracheal intubation. *Anesthesiology*. (2007) 106:916–23. doi: 10.1097/01.anes.0000265150.71319.91

41. Connor CW, Segal S. Accurate classification of difficult intubation by computerized facial analysis. *Anesth Analg*. (2011) 112:84–93. doi: 10.1213/ANE.0b013e31820098d6

42. Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, et al. Practice guidelines for management of the difficult airway: an updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. (2013) 118:251–70. doi: 10.1097/ALN.0b013e31827773b2

43. Han R, Tremper KK, Kheterpal S, O'Reilly M. Grading scale for mask ventilation. *Anesthesiology*. (2004) 101:267. doi: 10.1097/00000542-200407000-00059

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 16 August 2023
DOI 10.3389/fmed.2023.1216538

OPEN ACCESS

EDITED BY
Antonio M. Esquinas,
Hospital General Universitario Morales Meseguer, Spain

REVIEWED BY
Meryl Vedrenne,
Hôpital Necker-Enfants Malades, France
Peter Oishi,
University of California, San Francisco, United States

*CORRESPONDENCE
Robert P. Richter
✉ rrichter@uabmc.edu

RECEIVED 04 May 2023
ACCEPTED 21 July 2023
PUBLISHED 16 August 2023

CITATION
Webb L, Burton L, Manchikalapati A, Prabhakaran P, Loberger JM and Richter RP (2023) Cardiac dysfunction in severe pediatric acute respiratory distress syndrome: the right ventricle in search of the right therapy. *Front. Med.* 10:1216538. doi: 10.3389/fmed.2023.1216538

Cardiac dysfunction in severe pediatric acute respiratory distress syndrome: the right ventricle in search of the right therapy

Lece Webb[1], Luke Burton[1], Ananya Manchikalapati[2], Priya Prabhakaran[1], Jeremy M. Loberger[1] and Robert P. Richter[1]*

[1]Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL, United States, [2]Division of Pediatric Critical Care, Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, United States

Severe acute respiratory distress syndrome in children, or PARDS, carries a high risk of morbidity and mortality that is not fully explained by PARDS severity alone. Right ventricular (RV) dysfunction can be an insidious and often under-recognized complication of severe PARDS that may contribute to its untoward outcomes. Indeed, recent evidence suggest significantly worse outcomes in children who develop RV failure in their course of PARDS. However, in this narrative review, we highlight the dearth of evidence regarding the incidence of and risk factors for PARDS-associated RV dysfunction. While we wish to draw attention to the absence of available evidence that would inform recommendations around surveillance and treatment of RV dysfunction during severe PARDS, we leverage available evidence to glean insights into potentially helpful surveillance strategies and therapeutic approaches.

KEYWORDS

children, pediatric acute respiratory distress syndrome (PARDS), right ventricular (RV) dysfunction, echocardiography (Echo), extracorporeal membrane oxygenation (ECMO)

Introduction

Acute respiratory distress syndrome (ARDS) in children, or pediatric ARDS (PARDS), is a common but severe manifestation of a host of insults to the respiratory system of a child that carries a significant risk of morbidity and mortality (1). As in a patient of any age, ARDS involves direct and/or indirect mechanisms that disrupt the protective surface tension along the apical surface of alveolar cells, flood alveoli with cellular debris, and promote pulmonary interstitial disruption through leukocyte recruitment and local microvascular endothelial leakage. Together, the resultant lung pathobiology leads to a clinical syndrome of respiratory system failure with hypoxemia and hypercapnia that can cascade into multiorgan failure and late death (2).

In our experience, right ventricular (RV) dysfunction and eventual failure is an important, and often occult, driver of multiorgan failure in the setting of PARDS. Though RV dysfunction is a well-known phenomenon described in adult ARDS literature, evidenced by various reviews on the topic in recent years (3–6), there is a dearth of literature on the topic in children. The purpose of this narrative review is thus two-fold. First, we wish to bring a greater awareness of this under-recognized disease process to the pediatric critical care community. Second, we are issuing a clarion call for pediatric researchers to improve our understanding of the incidence of and mechanisms driving this disease. It is our hope that by calling greater attention to the

often-neglected right heart, we may substantially improve outcomes in children with PARDS.

PARDS definition and evidence-based management

Though operational definitions for ARDS have existed for adults for decades (7–9), their validity in children had not been formally tested and thus remained limited in this population. Researchers within the Pediatric Acute Lung Injury and Sepsis Investigators network convened the Pediatric Acute Lung Injury Consensus Conference (PALICC) to gain consensus on the first pediatric-focused definition of ARDS (10). Together, the collaborators acknowledged the essential role that mean airway pressure plays in driving oxygenation and thus implemented the oxygenation index to stratify PARDS instead of a PaO_2/F_IO_2 ratio. The Consensus Conference also recognized that use of arterial oxygen sampling is not homogeneous across pediatric intensive care units (PICU) and thus incorporated oxyhemoglobin data from pulse oximetry into the determination of PARDS severity when PaO_2 data are unavailable. The PALICC experts simplified the radiological criteria for PARDS to any radiographic evidence of alveolar disease rather than "bilateral opacifications" on chest imaging as recommended in the Berlin criteria. Unique to the PALICC definition, PARDS could be described in specific pediatric populations with pre-existing comorbidities such as chronic lung disease and cyanotic heart disease.

Lung protective ventilation using low tidal volume and higher positive end-expiratory pressure-to-fraction of inspired oxygen ($PEEP/F_IO_2$) ratios became standard management of ARDS in adults following the first ARDS Network trial in 2000 (11). Until the last decade, PARDS management subsisted without consensus recommendations and remained at the discretion of individual PICU providers. In 2015 and largely informed by the ventilator strategy described by the ARDS Network, PALICC published the first consensus recommendations for the management of PARDS (10). This has been followed by a very recent update published in February 2023 focusing on emerging evidence and resource-limited settings but generally carried forward the same recommendations as described in 2015 (12).

For the typical patient with severe PARDS, standard ventilator management consists of low tidal volume ventilation (4–6 mL/kg of ideal body weight) and higher $PEEP/F_IO_2$ ratios with the express intent of limiting plateau pressure to below 28 cmH_2O, limiting driving pressure (defined as plateau pressure minus PEEP) to less than 15 cmH_2O, and preserving functional residual capacity (FRC) by preventing atelectasis (13). However, PARDS manifests along a spectrum of phenotypes and severity (14). Moreover, the respiratory system of a critically ill child with PARDS must managed within the context of the entire patient, most especially considering the interactions between intrathoracic pressure changes and cardiovascular function (see next section for more detail). For example, to achieve the afore-mentioned ventilatory targets, it is common practice to accept permissive hypoxemia and hypercapnia for a patient with severe PARDS in an effort to limit ventilator-induced lung injury with recommended lower limits of oxygen saturations and arterial pH of 88% and 7.20, respectively (12, 13). However, the ensuing hypoxemia, hypercapnia, and acidemia, in tandem with the disturbance in normal lung architecture from regional atelectasis or alveolar overdistention, increases pulmonary vascular resistance (PVR) and RV afterload (Figure 1) that may prove harmful for children with limited capacity to handle acute changes in RV end-diastolic pressure (RVEDP) or volume (RVEDV). Though the authors of the PALICC-2 guidelines acknowledge the potential for lung-protective interventions to impact biventricular function, further research is needed to more clearly define ideal management of the right heart concurrent with lung-protective strategies (12, 15).

Right heart dysfunction during PARDS

Anatomy and physiology of the pediatric RV in health and disease

The human heart undergoes developmental changes throughout childhood that are important to consider in the management of PARDS (see Table 1). *In utero*, high PVR facilitates the redirection of systemic and placental venous return away from the lung through either the ductus arteriosus or the foramen ovale for eventual ejection to the systemic circulation. As the morphologic RV (assuming situs solitus with levocardia and D-looped ventricles) is conditioned by elevated PVR *in utero*, RV and left ventricle (LV) wall thicknesses are nearly identical at birth (16). As the PVR drops postnatally with a neonate's first breaths, RV afterload rapidly declines. This permits the gradual reconditioning of the RV in a low pressure environment that results in thinning of the RV wall mass over the ensuing weeks-months of infancy.

At a cellular level, myocardial fibers of the neonatal and young infant's heart globally have higher connective tissue-to-contractile protein ratios with generally fewer and less organized myofibrils present per cardiomyocyte (17). This myofibril anatomy compromises the ability of the cardiomyocyte to both contract and to relax, leading to a state of minimal systolic and diastolic reserve. The transverse tubules and sarcoplasmic reticula overlying myofibrils within cardiomyocytes are also immature in the young infant, further limiting the calcium-dependent inotropic capacity of the infant's myocardium and rendering the myocardium reliant upon extracellular calcium sources for sarcomeric contraction. Moreover, the neonatal heart has a higher preponderance of parasympathetic innervation with lower β-adrenergic receptor expression compared to older children or adults, limiting RV and LV contractile reserve.

The density and anatomic arrangement of RV fibers also contribute to the limited contractile reserve of the RV. In contrast to the LV that is comprised of three myocardial fiber layers with complex alignment permitting torsional constriction of the LV cavity, the RV is generally made up of only superficial and deep layers of muscle fibers (18). The superficial myofibers are predominantly transversely oriented, blending into the superficial myocardial layer of the ventricular septum and LV, while the deeper myofibers are more longitudinally aligned (18). Given the lower postnatal wall stress perceived by the RV, each myocardial fiber within the RV carries a substantially reduced number of mitochondria (19). These factors together limit RV contractile capacity and metabolic reserve at baseline in both neonates and younger children.

In older children as in adults, the RV generally has a greater capability of tolerating sudden myocardial demands (e.g., increases in

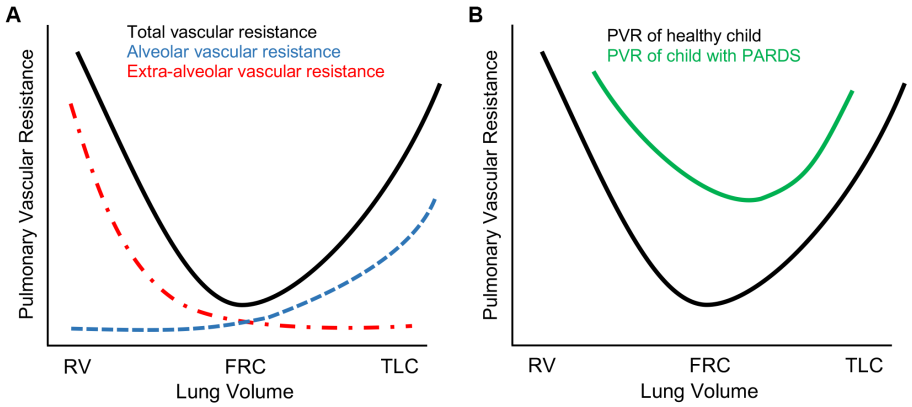


FIGURE 1
Pulmonary vascular resistance (PVR) changes in severe pediatric acute respiratory distress syndrome (PARDS). **(A)** Schematic representation of total PVR as a function of lung volume in a healthy pediatric lung. PVR is lowest at functional residual capacity (FRC) and highest either at residual capacity (RV) where PVR is elevated due to resistive changes in extra-alveolar vasculature or total lung capacity (TLC) where PVR is elevated due to resistive changes in alveolar vasculature. **(B)** In severe PARDS, PVR is globally elevated secondary to a complex combination of the following: (1) lung architectural heterogeneity from regional atelectasis, alveolar overdistention, or parenchymal cystic changes; (2) hypoxia-, hypercapnia-, and acidemia-mediated vasoconstriction; (3) parenchymal inflammatory changes with associated pulmonary edema.

TABLE 1 Differences in myocardial cellular anatomy and cardiopulmonary physiology between neonates and older children/adults.

Variable	Neonate/young infant	Older child/adult	Effect on right ventricle
Pulmonary vascular resistance	↑	↓	• Afterload, myocardial stress (systolic function)
Cardiac myocyte connective tissue-to-contractile protein ratio	↑	↓	• Contractility (systolic function) • Wall stiffness (diastolic function)
Myofibril organization in cardiac myocyte	Disorganized, not uniformly linear	Mature, linear alignment	• Contractility (systolic function)
Development of transverse tubules and sarcoplasmic reticula	Underdeveloped	Mature	• Neonate: reliance on extracellular sources of Ca^{2+} for myofibril contraction • Older child: well-synchronized Ca^{2+}-induced Ca^{2+} release from sarcoplasmic reticula in response to cardiomyocyte membrane depolarization, facilitating coordinated myofibril contraction
Myocardial β_1-receptor expression	↓	↑	• Contractility (systolic function)

preload and/or afterload) than neonates through elevations in heart rate, contractility, and stretch to accommodate the increased RVEDV. Moreover, extrapolating from canine models of acute afterload changes to the ventricles, LV contractility may contribute 20%–40% of RV output in older children through ventricular tethering (20). In neonates, such a demand on the RV is not as well tolerated. In addition to the cellular and anatomic differences in the neonatal myocardium described above, the resting heart rate of neonates is typically higher than older children. Thus, the "therapeutic window" by which neonatal heart rates can elevate to generate a compensatory increase in cardiac output before tachycardia limits ventricular filling is narrower than older children. Additionally, the PVR in some infants may remain elevated for the first several months of life, increasing basal afterload on the RV. In children with persistently elevated PVR from birth as seen in bronchopulmonary dysplasia or congenital heart diseases with pulmonary over-circulation, the poorly compliant RV is able to gradually adapt to the higher levels of wall stress through myocardial hypertrophy. However, this compensatory mechanism comes at the cost of further limiting RV diastolic function (21).

Given the limited contractile reserve of the RV in an older child, acute increases in RVEDV are initially tolerated through modest dilation of the relatively compliant RV wall. As greater stress is placed on the RV myocardium through increasing afterload and/or preload and myofibrils are stretched further, myosin-actin interactions are reduced and systolic function becomes embarrassed (extreme of the Frank–Starling relationship). The reduction in RV contractility is thus

unable to respond to the increased preload by raising, or even maintaining, stroke volume. The ensuing acute RV dilation can cause a precipitous compression of the LV through ventricular interdependence. In combination with diminished pulmonary venous return due to limited RV output and reduced pulmonary blood flow, LV compression can result in an embarrassment to systemic cardiac output—a process termed acute cor pulmonale (ACP). The combination of increased RV wall stress and decreased systemic cardiac output can result in coronary ischemia that further reduces RV systolic function that can culminate in cardiac arrest.

During PARDS, the developing heart of a neonate or young infant is rather suddenly exposed to a potentially toxic cardiorespiratory milieu. Intrathoracic positioning intrinsically subjects the right atrium and RV to transpulmonary pressures changes. During positive pressure ventilation with high mean airway pressures, right atrial filling is limited due to a reduction in transmural pressure, which may decrease RV preload (though this effect may be diminished as lung compliance worsens). While positive pressure ventilation generally reduces transmural pressures across both ventricles (which would be expected to reduce ventricular afterload and metabolic demand), increases in PVR observed during PARDS can overwhelm the modest reduction in RV afterload and stress the RV myocardium. As PARDS severity worsens, PVR rises due to hypoxia-/hypercarbia-mediated vasoconstriction, reduction in recruited alveolar units, and higher mean airway pressures generated in an effort to sustain systemic oxygenation. These stressors to the RV are not easily correctable. The RV of an older child generally has the capacity to handle acute increases in RVEDP and RVEDV by mounting an increase in RV contractility and moderate dilatation (Figure 2). As discussed above, the neonatal myocardium has much less ability to respond to acute changes in volume and pressure experienced during severe PARDS.

RV dysfunction: definition, incidence, and evaluation

To the credit of the PALICC investigators, the RV is mentioned as a potential culprit worthy of interrogation in the setting of "suspected cardiac dysfunction" during PARDS (10). Unfortunately, absence of a formal definition for RV dysfunction in children precludes uniform diagnosis or management. Even in adult practice, precise definitions for RV dysfunction and RV failure remain elusive. These pathophysiologic manifestations may be more practically distinguished by the RV myocardial response to increased RVEDV, as offered by Vieillard-Baron et al. (23) (Figure 2). In states of RV dysfunction, though myocardial contractility may be impaired, the ventricle is able mount a response to higher preload by increasing, or at least maintaining, stroke volume without developing systemic venous congestion. As RV systolic function deteriorates, the RV is unable to increase or maintain stroke volume in response to incremental increases in RVEDV, leading to impaired RV outflow. In this state of RV failure, reduced RV output cascades into lower LV preload; systemic-to-suprasystemic RVEDP with resultant RV ballooning, LV compression, and tricuspid regurgitation; and ultimately systemic venous congestion with reduced end-organ perfusion.

While a general gestalt exists amongst pediatric cardiologists and intensive care providers, an objective, operational definition of pediatric RV dysfunction or failure remains elusive for a number of important reasons. First, there is not a consensus among pediatric cardiologists regarding whether RV dysfunction should be categorized according to systolic dysfunction, diastolic dysfunction, or both. Second, while most pediatric cardiologists and pediatric intensive care providers would agree that a battery of biomarkers and echocardiographic data are essential to diagnosing RV dysfunction at the bedside, the precise assays and ultrasonic readouts required for diagnosis continue to be debated. Moreover, many echocardiographic measures commonly employed to determine RV function in adults remain unvalidated in children and are rarely performed by pediatric sonographers.

Epidemiology

Early and persistent RV hypertension and dysfunction have been associated with higher mortality in children with ARDS (24, 25). However, as uniform definitions for RV dysfunction, RV failure, and ACP remain unclear at this time, it is difficult to accurately report the incidence of or risk factors for PARDS-associated RV dysfunction. Therefore, we must again lean on literature from adult ARDS populations to begin understanding the prevalence of this disease. Two separate prospective cohort studies report incidences of the severest form of RV failure, acute cor pulmonale (ACP), to be nearly 20% during moderate-to-severe ARDS managed with protective lung ventilation (26, 27). Thus, it is reasonable to postulate that RV dysfunction is present in nearly 1 out of every 4 children with moderate-to-severe PARDS and that RV failure is an important driver of PARDS-associated mortality.

In adults with ARDS, risk factors for developing ACP include pneumonia as the etiology for ARDS, PaO_2/F_IO_2 ratio <150 mmHg, $PaCO_2$ ≥48 mmHg, and driving pressure ≥18 cmH_2O (27). Though further research is warranted to characterize discrete risk factors for RV dysfunction and failure in PARDS, given a recent series of RV failure in infants with bronchopulmonary dysplasia admitted to our institution for PARDS, PICU providers at our center have adopted a policy of greater vigilance for RV dysfunction in children with underlying cardiopulmonary disease (e.g., congenital heart disease, bronchopulmonary dysplasia, sickle cell anemia, chronic kidney disease with long-standing hypertension) who develop severe PARDS. Moreover, our institute has adopted a policy in which development of multiorgan failure during PARDS immediately prompts interrogation of RV function as a potential cause of end-organ damage. In light of the paucity of evidence around the incidence and risk factors for PARDS-associated RV dysfunction, it is imperative that the American Society of Echocardiography and European Association of Cardiovascular Imaging settle on a formal definition of RV dysfunction for PARDS epidemiologic reporting purposes and for future PARDS research initiatives.

Clinical signs and biomarkers

In the absence of consensus recommendations, many pediatric centers rely upon complementary exam findings, noninvasive and invasive monitoring readouts, and biomarker data, in concert with echocardiographic measures of RV performance, to identify RV dysfunction. Clinical exam findings that might suggest RV dysfunction during PARDS include persistent atrial tachycardia in the presence of

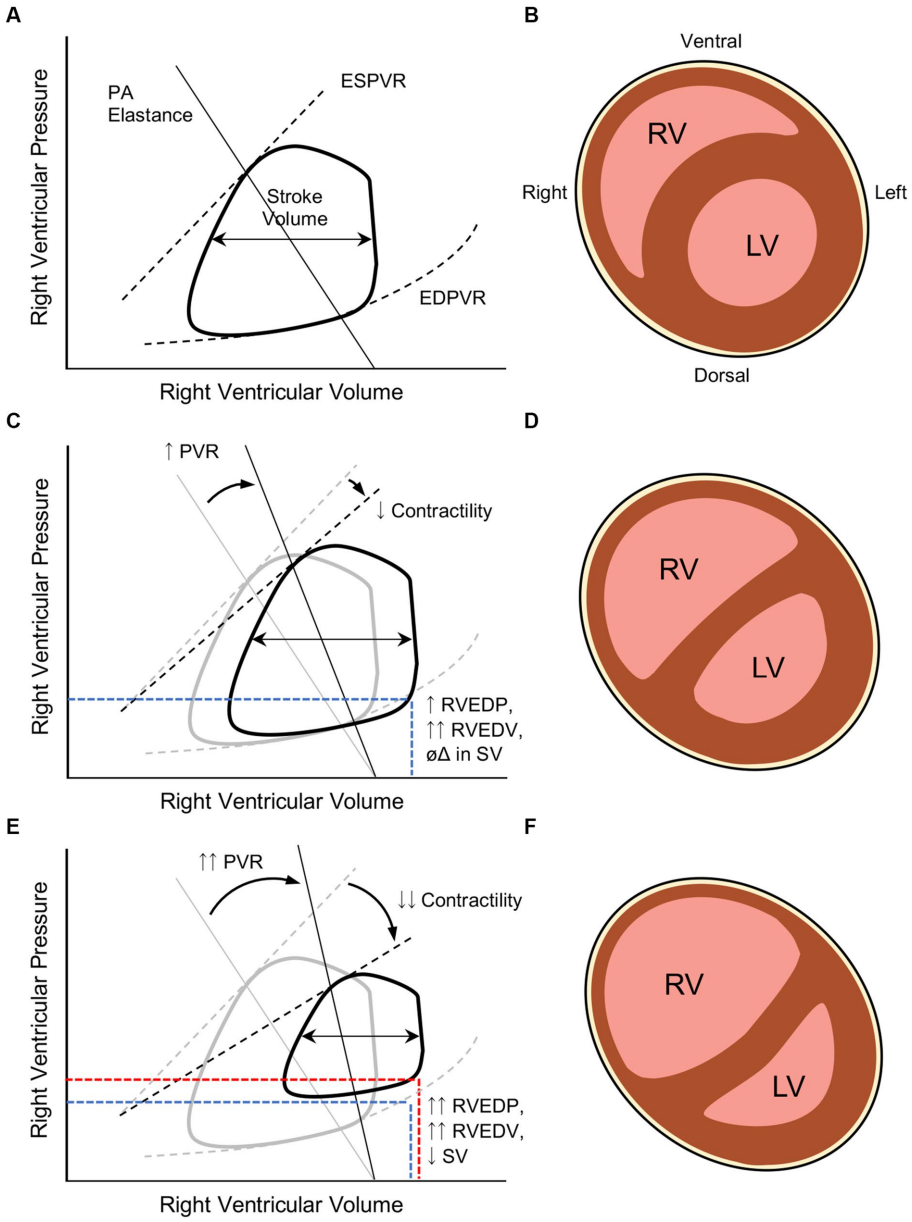


FIGURE 2
Pathophysiologic changes in right ventricular (RV) systolic and diastolic function during severe pediatric acute respiratory distress syndrome (PARDS). **(A)** Normal RV end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively) in a healthy child as a function of pulmonary arteriolar (PA) elastance that generates a given stroke volume (difference in RV end-systolic and end-diastolic volumes, or RVESV and RVEDV). Adapted from Brener et al. (22). **(B)** After the first several months of life, the RVEDP is significantly lower than the LVEDP in a healthy child, leading to the RV taking a more crescentic shape around the LV (cartoon transverse cross-section of a situs solitus heart with D-looped ventricles). **(C)** In severe PARDS, increases in PVR result in higher RV afterload that, in a developing heart, can precipitate RV systolic dysfunction that manifests with impaired contractility. The result of these pathologic changes result in higher RVEDP and RVEDV; however, stroke volume (SV) is preserved. **(D)** Elevated RVEDP and RVEDV begins to dilate the RV and compete against LVEDP, leading to ventricular septal flattening. **(E)** In the setting of RV failure, the RV does not adapt to the higher RVEDV and begins to manifest lower stroke volumes. **(F)** The much higher RVEDP begins to reach or surpass LVEDP and impose upon LVEDV. The diminished LV preload from both a reduction in RV output and RV compression can compromise systemic cardiac output and coronary artery perfusion. RV ballooning will also result in tricuspid regurgitation and elevated systemic venous pressures, compromising perfusion pressures of end-organs.

preserved LV systolic function, rising central venous pressure (CVP), and inspiratory pulse pressure variation (reverse pulsus paradoxus) on invasive arterial pressure monitoring that is unresponsive to volume expansion. Children with RV dysfunction commonly develop acute hepatomegaly that can result in abdominal distention and worsening respiratory system compliance from thoraco-abdominal competition. Anasarca that is unrelated to fluid overload manifests due to a persistently elevated CVP that leads to elevated hydrostatic pressures in peripheral microvascular beds. Similarly, high CVP may reduce lymphatic drainage into the subclavian veins that can result in pleural effusions and ascites. Feeding intolerance manifest as a reduction in intestinal perfusion pressure and due to the peritoneal space occupation by severe hepatomegaly. Elevated plasma levels of brain-type natriuretic peptide (BNP) or N-terminal pro-BNP are sensitive

but nonspecific markers of RV wall stretch and, in the absence of frank renal failure, are commonly employed to evaluate for RV wall stress and right atrium/RV dilation (28–30). Climbing plasma levels of direct bilirubin and creatinine may point to decompensation in liver or renal perfusion pressures, respectively, as a result of elevated right-sided heart pressures with back-filling of the vena cavae. Recognition of any of these clinical markers in a child with PARDS should prompt echocardiographic assessment of RV size and function.

Ultrasound evaluation

Ultrasonographic assessment, both by formal comprehensive echocardiography and by point-of-care ultrasound, is now one of the hallmark methods for diagnosing RV dysfunction in PARDS. In the PICU, transthoracic echocardiography (TTE) is most commonly employed because of its noninvasive approach and capability of being performed at the bedside by a sonographer without the express need for a cardiologist present. TTE also affords the ability for serial examination of the heart in concert with dynamic changes during the course of PARDS. However, adequate acoustic windows can be challenging to acquire during PARDS, and the retrosternal position of the RV may further complicate proper image acquisition. Table 2 summarizes reported echocardiographic readouts of RV performance and their advantages/disadvantages.

The American Society of Echocardiography recommends both qualitative and at least one quantitative assessment to determine RV systolic function in adults (31). Though the American Society of Echocardiography offer various quantification protocols for evaluating pediatric RV function, formal recommendations are less well developed (32, 33). RV performance can be measured by ventricular dimension changes, wall strain pattern, and doppler readouts throughout the cardiac cycle.

Due to its complex geometry, singular measurements of linear dimensions are rarely sufficient functional readouts, and commonly used measures of LV function (e.g., shortening fraction, ejection fraction) are unreliable with two-dimensional sonography of the RV. Qualitatively, using an apical 2 or 4 chamber view, RV diameter can be grossly, though subjectively, compared to LV diameter. This assessment may be further quantified as the RV/LV end-systolic diameter ratio. In older children (average age ~8.5 years), normal RV/LV ratios have been reported to be <0.6 with values >1 being associated RV hypertension and adverse clinical outcomes (34). Qualitative assessment of the interventricular septum can be performed in the parasternal short axis: flattening of the septum and a D-shaped LV in this view are indicative of RV hypertension and elevated RVEDV. Enlargement of the right atrium and inferior vena cava with limited respiratory variation in the diameter of the inferior vena cava can point to elevated RVEDP, resulting in limited RV filling and venous congestion. However, these measures provide only a vague estimation of elevated RV pressures. Furthermore, as pulmonary arteriolar resistance may require 6–12 months to reduce to normal adult-like physiology following birth, further work is needed to generate validated ratios in neonates and infants.

To begin quantitative assessment of RV function, pediatric cardiologists commonly measure peak velocity of the tricuspid insufficiency jet during systole (V_{TI}) using continuous-wave doppler. When combined with an average CVP measured in the superior vena cava or right atrium, this peak velocity can provide a more objective measure of systolic pressures the RV is capable of mounting [RV systolic pressure = average right atrial pressure + $4^*(V_{TI})^2$]. Longitudinal shortening can be measured quantitatively using tricuspid annular plane systolic excursion (TAPSE) (35). TAPSE is best evaluated in an apical 2 or 4 chamber view employing M mode to track the distance moved by the lateral tricuspid valve annulus in a single cardiac cycle. In adults, TAPSE ≥18 mm is considered normal while <17 mm is highly suggestive of systolic dysfunction (36). There are TAPSE values indexed to body surface area that can be referenced for pediatric patients (37); however, this readout is infrequently measured and reported in pediatric echocardiography and specific *Z* score values for children remain unvalidated.

Fractional area change of the RV can also provide a quantitative measure of systolic function. In the apical view, the RV cavity is traced and measured in end-diastole and end-systole. A reduction of at least 1/3 of the area from diastole to systole suggests normal RV systolic function in adults (38). However, validated, normal values for children are unknown. Moreover, accuracy of the RV fractional area change to predict RV systolic function diminishes as RVEDV increases (39).

RV wall strain pattern has become a helpful adjunct to diagnose RV systolic dysfunction in adults (40, 41). A recent report by Romanowicz et al. (42) provides validated RV strain values and *Z* scores for children using two-dimensional speckle tracking echocardiography, which may prove helpful in quantifying RV systolic function during PARDS in the years to come. However, until RV strain measures are more consistently performed by pediatric cardiologists and reported strain values are more widely circulated in literature, the utility of employing RV strain values to diagnosis new or persistent RV systolic dysfunction during PARDS remains unknown.

In addition to changes in RV geometric dimensions or RV wall strain, various doppler measurements of RV performance may have utility in diagnosing RV systolic and/or diastolic dysfunction during PARDS. Tissue doppler imaging of the RV free wall at the level of the tricuspid annulus can be used to measure myocardial systolic peak velocity (s′), early diastolic velocity (e′), and late diastolic velocity (a′); together, these readouts provide valuable real-time information on RV myocardial contractility and relaxation. To corroborate RV s' data and detail RV systolic function, sonographers may capture the isovolumetric acceleration of the basilar aspect of the RV free wall that can provide more specific information on RV longitudinal shortening. Myocardial performance index (Tei index), measured as the sum of the duration of the cardiac cycle in RV isovolumetric contraction and relaxation divided by the duration of RV ejection, may provide a sensitive readout suggestive of either RV systolic or diastolic dysfunction. Finally, in the presence of tricuspid insufficiency, changes in tricuspid regurgitation velocity can be measured and reported as a change in pressure over change in time (dP/dt), approximating the rate of rise in RV pressure during early systole reflective of RV systolic performance. Though each of these advanced imaging modalities may eventually prove useful (or even essential) in diagnosing RV dysfunction in the setting of PARDS in the future, their availability and scope of use outside the management of congenital heart disease remain quite limited.

Therapeutic strategies for RV dysfunction during PARDS

Little evidence can be amassed to guide the treatment for PARDS-mediated RV dysfunction, leaving the pediatric

TABLE 2 2D echocardiographic measures of right ventricular function during PARDS (31, 32).

Metric	Functional measure	Strength	Weakness
Dimension changes			
RA diameter	Diastole	• Commonly evaluated	• Less helpful without prior echocardiographic measurement • Preload-dependent
IVC size, respiratory variation	Diastole	Same as above	• Subjective • Preload-dependent
Interventricular septal position	Diastole	Same as above	Same as above
RV-to-LV end-systolic diameter ratio	Diastole	• Easy to measure	• Less commonly evaluated in children • Difficult to visualize lateral wall • May poorly predict RV volume changes
TAPSE	Systole	• May correlate with RV ejection fraction • Easy to measure • Quantitative read-out	• Less commonly evaluated in children • Preload-dependent • *Z* scores unvalidated in children
Fractional area change[a]	Systole	• Improvement over linear dimension changes • Quantitative read-out • Adult data available	• Preload-dependent • Difficult to visualize lateral wall • Unvalidated in children
Wall strain pattern			
2D speckle tracking	Systole	• Less preload-dependent	• Dependent on probe alignment • High noise-to-signal ratio • Requires additional software and complex analysis • Unvalidated in children
Doppler			
Tricuspid insufficiency peak velocity (V_{TI})[b]	Systole	• Commonly evaluated • Quantitative read-out	• Dependent on probe alignment • Less commonly evaluated in children • Preload-dependent • Reliant on tricuspid insufficiency
d*P*/d*t*[c]	Systole	• Quantitative read-out	Same as above
Myocardial performance index[d]	Systole, diastole	• Quantitative read-out • Adult data available	• Dependent on probe alignment • Less commonly evaluated in children • Preload-dependent
Isovolumetric acceleration	Systole	• Quantitative read-out	Same as above
Tissue doppler imaging	s: systole e′, a′: diastole	• Easy to measure • Pediatric data available	Same as above

2D, two-dimensional; d*P*/d*t*, rate of rise of intraventricular pressure during isovolumetric contraction; IVC, inferior vena cava; LV, left ventricle; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion. [a]Fractional area change of RV is determined by the formula: (end-diastolic area − end-systolic area)/end-diastolic area.
[b]V_{TI} is used to approximate peak RV systolic pressure by the formula: average right atrial pressure + 4*(V_{TI})^2.
[c]d*P*/d*t* (mmHg*sec^{-1}) is determined by measuring the time (milliseconds) required to progress from an initial velocity (V_1, m*sec^{-1}; typically 1 m*sec^{-1} is used) to a second velocity (V_2, m*sec^{-1}; typically 2 m*sec^{-1} is used) tricuspid insufficiency envelope detected by continuous-wave doppler. d*P*/d*t* is then calculated by the formula: [(4*V_2^2) − (4*V_1^2)]/(time*0.001). For example, if 25 milliseconds are required for a tricuspid insufficiency jet velocity profile to increase from 1 m*sec^{-1} to 2 m*sec^{-1}, d*P*/d*t* is equal to [(4*2^2) − (4*1^2)]/(25*0.001), or 480 mmHg*sec^{-1}.
[d]Myocardial performance index is determined by the formula: (time in isovolumetric contraction + time in isovolumetric relaxation)/duration of RV ejection.

intensivist to rely on evidence for treating RV dysfunction in the setting of other etiologies, extrapolation from literature in adult populations, and/or on basic understanding of cardiopulmonary pathophysiology during PARDS. Here we will summarize the most frequently used therapeutic strategies for treating RV dysfunction during PARDS and their supporting evidences

TABLE 3 Proposed therapies for right ventricular dysfunction in pediatric acute respiratory distress syndrome.

Therapy	Purpose and mechanism	References
MV strategies	↓ PVR by:	
Limit driving pressure	↓ RV afterload	
Titrate mean airway pressure	Restore FRC, ↑ PaO_2 ➔ pulmonary vasodilation	
↑ F_IO_2	↑ PaO_2 ➔ pulmonary vasodilation	
↑ Minute ventilation	↓ $PaCO_2$ ➔ pulmonary vasodilation	
Prone posture	↓ PVR and RV afterload by:	(43–45)
	↓ Ventral-to-dorsal transpulmonary pressure gradient ➔ ↑ alveolar V/Q matching	
	↑ Respiratory system compliance ➔ ↓ driving pressure	
	Optimizing RV geometry	
Pulmonary vasodilators	↓ RV afterload by ↓ PVR	(46–48)
Inhaled nitric oxide	Guanylate cyclase activator	
Inhaled epoprostenol, iloprost	PGI_2-receptor agonist	
Milrinone	PA PDE-3 inhibitor	
Inotropic agents	Increase RV, LV contractility	(46, 49)
Epinephrine, dobutamine	Myocardial β_1-receptor agonist	
Milrinone	Myocardial PDE-3 inhibitor	
Ca^{2+} (neonates)	Bind troponin C, exposing myosin binding sites on actin	
Vasoactive agents	Increase SVR and coronary perfusion pressure	(46, 50, 51)
Norepinephrine	Systemic arteriolar α_1-receptor agonist	
Vasopressin	Systemic arteriolar V_1-receptor agonist May ↑ NO in PAs and thus ↓ PVR	
Fluid management	Judiciously ↓ RVEDP by ↓ RVEDV	(52, 53)
Loop, thiazide diuretics	Sodium and free water excretion	
CRRT	Plasma ultrafiltration	
ECMO	Rescue therapy	
VV	↓ PCO_2 and ↑ pH, PO_2 in PAs	
VA/VP	↓ RV preload and thus ↓ RVEDP Maintain systemic oxygen delivery in a failing RV	

cAMP, cyclic adenosine monophosphate; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; FRC, functional residual capacity; MV, mechanical ventilation; NO, nitric oxide; PA, pulmonary artery; PCO_2, partial pressure of carbon dioxide; PDE-3, phosphodiesterase 3; PO_2, partial pressure of oxygen; PVR, pulmonary vascular resistance; RV, right ventricle; RVEDP, right ventricular end-diastolic pressure; SVR, systemic vascular resistance; VA, venoarterial; VP, veno-pulmonary arterial; V/Q, ventilation/perfusion; VV, venovenous.

(Table 3), focusing on (1) reduction of RV afterload, (2) restoration and sustenance of RV contractility, and (3) optimization of RV diastolic function. However, the prioritization and urgency for implementing these RV protective strategies remains unknown at this time.

Mechanical ventilation management

There is little evidence to guide the management of invasive ventilation when RV dysfunction is suspected or confirmed in a child with PARDS beyond PALICC recommendations. Informed by clinical data from ARDS studies in adults (3), it is reasonable to employ the following strategies to reduce PVR and RV afterload. As oxygen is a selective pulmonary vasodilator, F_IO_2 may be temporarily increased and mean airway pressure judiciously titrated to optimize dynamic compliance or respiratory system impedance (assuming negligible contribution of airway resistance to the patient's respiratory mechanics) in an effort to preserve FRC (thus maximizing alveolar recruitment while limiting regional dead-space) and drive oxyhemoglobin saturation above 90%. Caution is warranted here as prolonged exposure to high F_IO_2 may contribute to ventilator-induced lung injury, and exposure to high mean airway pressure without re-evaluation of RV performance may precipitate further RV decline. Permissive hypercapnia goals should be tightened, though a precise upper limit of $PaCO_2$ is unclear at this time. Acidemia should be corrected either with judicious increases in minute ventilation (while limiting driving pressure) and/or with increased circulating levels of bicarbonate. There is insufficient evidence to support mode of ventilation (e.g., conventional mechanical ventilation, high frequency oscillatory ventilation, airway pressure-release ventilation, etc.) to accomplish these goals, regardless of RV function (54). At present, it is unknown whether spontaneous respiratory effort is more advantageous for a dysfunctional RV during PARDS than neuromuscular blockade.

Prone posture

Prone positioning as a treatment for ARDS and a tool to decrease ventilator-induced lung injury is well-described in adults (55–58). It has also been shown to have a role in unloading the RV and improving right ventriculo-arterial coupling (43). Proning can decrease PVR and increase cardiac output among adult patients with ARDS (44). Vieillard-Baron et al. (45) demonstrated an increase in cardiac index with 18 h of prone positioning of patients with ARDS-induced ACP. Moreover, an adult cohort with severe ARDS randomized to prone posture experienced a significantly lower incidence of cardiac arrest relative to those who remained supine (55). There are several proposed mechanisms for the hemodynamic benefit of prone positioning that culminate in reduced RV afterload (43). Despite increasing dorsal transpulmonary pressure (as measured by esophageal manometry) (59), the prone posture may increase overall respiratory system compliance by reducing the ventral-to-dorsal transpulmonary pressure differential (60). This improvement in respiratory mechanics reduces driving pressures while increasing the homogeneity of alveolar ventilation (43), limiting risk of ventilator-induced lung injury and associated RV dysfunction (61, 62). Improvements in ventilation and oxygenation associated with more optimal ventilation/perfusion matching would be expected to reduce PVR. Moreover, greater homogeneity in lung aeration would be expected to improve FRC toward baseline. Even modest restoration in FRC could reduce PVR and thus decrease RV afterload. There is also speculation that proning optimizes RV three-dimensional geometry, leading to improved RV systolic function (45). Though the evidence and mechanisms by which prone positioning promotes reductions in RV stress during ARDS have only been demonstrated in adults (summarized nicely by Vieillard-Baron et al. (43)), in the absence of evidence in the pediatric population, prone positioning can be reasonably employed for children with or at risk for acute RV dysfunction in the setting of PARDS.

Pulmonary vasodilators

Much like the goal of reducing systemic vascular resistance (SVR) in the setting of LV systolic failure, therapies that directly target PVR reduction are logical to prescribe in the setting of PARDS-related RV systolic dysfunction. The most commonly prescribed first-line treatment for increased PVR during PARDS is inhaled nitric oxide (iNO) (46) given its demonstrable reduction of PVR in adults with ARDS (63). Mechanistically, iNO induces pulmonary arterial vasodilation in regions of well-ventilated lung by stimulating guanylate cyclase in pulmonary arteriolar smooth muscle cells to generate cyclic guanosine monophosphate (64). However, despite evidence that iNO improves oxygenation during PARDS, children do not perceive a survival benefit with its use (65). Though other inhaled pulmonary vasodilators [e.g., inhaled epoprostenol (or prostacyclin) and iloprost (a synthetic analog of prostacyclin)] may have similar effects on PVR and systemic oxygenation as iNO, these therapies are intensely potent and may result in rebound pulmonary arterial hypertension if inadvertently discontinued. Therefore, their use in the PICU remains restricted to the management of isolated pulmonary hypertension without coincident PARDS (46–48).

Orally administered systemic vasodilators, such as sildenafil (phosphodiesterase 5 inhibitor), ambrisentan (endothelin receptor antagonist), bosentan (endothelin receptor antagonist), and riociguat (stimulator of guanylate cyclase), are typically utilized in children with chronically elevated PVR from diseases such as bronchopulmonary dysplasia, congenital heart disease, or sickle cell anemia (47, 66). In children with known pulmonary disease who present to the PICU with severe PARDS, critical care providers commonly continue these home therapies even in the absence of RV dysfunction for the hemodynamically stable child. Alternatively, in the previously healthy child now presenting with severe PARDS, our experience suggests that these therapies are not commonly considered unless the patient manifests persistent RV systolic dysfunction during a prolonged course of PARDS. In the face of a dearth of evidence to guide the use of inhaled or systemic vasodilators to treat or prevent RV systolic dysfunction during PARDS, these therapies cannot be universally recommended in all children with severe PARDS (10).

Inotropic and vasoactive agents

In the absence of robust evidence to support the use of inotropic or vasoactive agents for RV systolic dysfunction with PARDS, it is logical to reach for these therapies to sustain RV contractility and the LV contribution to RV output in an effort to maintain forward pulmonary blood flow and prevent RV bowing into the LV cavity. Low dose epinephrine (<0.05 μg/kg/min) or dobutamine (1–20 μg/kg/min) are catecholamines used to promote inotropy through β_1 G-protein coupled receptors with variable activity on pulmonary arterial vasodilatation through β_2-receptors (50, 67). The benefit of epinephrine and dobutamine over other inotropes (e.g., digoxin, milrinone) lies in their capacity for rapid titration. However, both catecholaminergic agents improve inotropy at the cost of increased myocardial oxygen demand.

Calcium is an important inotrope in an infant with RV dysfunction. Prior work has demonstrated that infants treated with intravenous calcium following cardiopulmonary bypass demonstrated significant improvements in cardiac output and mean systemic blood pressure compared to infants who did not receive calcium (68). Similarly, multiple case series attest to the incidence of myocardial dysfunction in infants manifesting nutrition-mediated hypocalcemia (69, 70). Physiologically, these findings may be explained by the underdeveloped t-tubular system of the myocardial sarcomere and an underdeveloped sarcoplasmic endoreticulum (evidence of which has been helpfully summarized by Baum and Palmisano (17)). The developmental immaturity of these myocardial structures demand that sarcomeric contractility in an infant's heart relies heavily on extracellular ionized calcium availability to facilitate myosin-actin interactions. Therefore, ensuring normal circulating levels of ionized calcium in young children may be necessary to sustain RV systolic function during PARDS. In a similar way, it may be logical to leverage the calcium-sensitizing effects of levosimendan to sustain or improve RV systolic function in a child with PARDS. However, the quality of evidence for the use of levosimendan in children with primary cardiac disease remains poor (71), and the evidence for levosimendan use outside of acute-on-chronic heart failure in children or adults is wholly lacking.

Milrinone may be considered in a hemodynamically stable children RV dysfunction due to PARDS. Milrinone is a phosphodiesterase 3 inhibitor, promoting pulmonary and systemic vasodilation along with myocardial inotropy by decreasing the degradation of cyclic adenosine monophosphate within vascular smooth muscle and myocardium, respectively. However, milrinone should be used with caution. It may promote global pulmonary vasodilatation that could worsen the respiratory shunt fraction and exacerbate systemic hypoxemia. Moreover, the long half-life and renal clearance of milrinone may precipitously lead to refractory hypotension in a child developing impaired renal function (72). In a hemodynamically unstable patient, milrinone is best used in conjunction with a vasopressor if used at all (49). In the setting of ACP, decreased SVR caused by milrinone could theoretically reduce LV end-diastolic pressure and paradoxically worsen LV compression by the ballooning RV (46).

Norepinephrine has been suggested in experimental models to improve RV function and cardiac output (4). By increasing SVR through the activation of α_1-receptors, norepinephrine raises the systemic diastolic pressure and thus may improve coronary perfusion. Norepinephrine also has mild activity on myocardial β_1-receptors that can improve both RV contractility and the LV contribution to RV cardiac output. In addition, norepinephrine increases LV afterload that results in higher LV end-diastolic pressures to compete against the rightward-shifting interventricular septum during RV failure (73). However, as with the use of epinephrine, care must be taken to recognize that norepinephrine will increase myocardial oxygen demand in an already stressed heart. Vasopressin, on the other hand, may be used in the hemodynamically unstable child with PARDS-mediated RV systolic dysfunction to maintain systemic arterial pressures without directly increasing myocardial oxygen demand. Vasopressin raises SVR by activating V_1-receptors in systemic arterioles, thus promoting increased intracellular calcium availability through the activation of phospholipase C. Importantly, vasopressin has a smaller effect on PVR than SVR (74). The mechanism is thought to be due to V_1-receptor-mediated nitric oxide release in the pulmonary vasculature that leads to vasodilation (51). Vasopressin has been shown to consistently decrease the pulmonary-to-aortic systolic pressure ratio in pediatric patients with known pulmonary hypertension (50). These properties suggest vasopressin as an ideal vasopressor choice in the setting of hemodynamically unstable RV systolic failure (46).

Fluid management

Fluid management during PARDS is a complex task. The conservative approach of fluid restriction and/or diuresis may reduce extravascular lung water and thus improve ventilation/perfusion matching; however, this may come at the cost of reduced intravascular volume and end-organ perfusion. Current recommendations for fluid management in the setting of PARDS focus on goal-directed care (neither conservative nor liberal in approach) (75). Typically, a child with normal biventricular function handles the significant changes in intravascular volume that occur between initial volume loading during resuscitation of shock and the aggressive diuresis that commonly follows cardiovascular stabilization in the setting of PARDS. However, RV function is particularly sensitive to the complex cardiopulmonary changes that occur with intravascular fluid shifts, especially during positive pressure ventilation with high mean airway pressure. An accurate assessment of intra- and extravascular volume status of a child in acute RV dysfunction is thus critical for preserving and/or restoring RV performance during PARDS.

The notion of preload dependence in a failing RV has merit, and increasing intravascular volume in an acutely hemodynamically unstable patient may be necessary. However, excess preload can worsen RV dilatation, resulting in septal bowing into the LV, tricuspid regurgitation with worsening venous congestion, and increased RV myocardial wall tension that compromises coronary perfusion pressure and may precipitate clinical decompensation (18, 52, 76–78). Though pulmonary arterial catheters are used exceedingly rarely in pediatrics, invasive monitoring using CVP trends can be helpful to guide the need for decongestion and to better understand the right atrial pressure necessary to provide adequate preload (53). Decongestion allows for decompression of the RV, reducing ventricular interdependence, and improving hemodynamics overall (49). Decongestion is primarily achieved through judicious diuresis, typically with the use of intravenous loop diuretics (e.g., furosemide, bumetanide) with or without the use of thiazide diuretics (e.g., intravenous chlorothiazide or, in children with sustained gut function, metolazone). There are many barriers to effective diuresis in patients with right heart dysfunction including acute kidney injury mediated by high CVP, low cardiac output, and the resulting reduction in renal perfusion pressure (79). In a hypervolemic patient with acute RV dysfunction, vasopressors may be required to sustain sufficient renal perfusion pressure while diuretic therapy is use to achieve RV decompression and venous decongestion (49). For children who fail to respond to diuretic therapy, continuous renal replacement therapy (CRRT) may be necessary to achieve intravascular volume removal (80). However, the need for CRRT in the setting of PARDS-associated RV dysfunction should heighten the pediatric intensivist's alertness to the patient's manifestation of extremis and impending cardiovascular collapse. In such a clinical situation, the ethical considerations and risks for deploying CRRT must be strongly weighed against any perceived benefit to the patient.

Extracorporeal membrane oxygenation

The decision to deploy extracorporeal membrane oxygenation (ECMO) for severe PARDS refractory to lung-protective ventilation is often challenging and emotionally charged. The pediatric intensivist often has to guide a family through the complex risks and benefits of deploying ECMO for their child in a time-sensitive manner with limited information. When RV dysfunction develops in the setting of severe PARDS, complex treatment decisions can become substantially more intricate. Here we would like to discuss (1) the decision to use venovenous (VV) versus venoarterial (VA) ECMO as the initial cannulation strategy for PARDS complicated by RV dysfunction and (2) specific treatment decisions around RV dysfunction during VV ECMO.

VV versus VA ECMO

Peripheral VV or VA ECMO are the predominant support modalities used to support children with severe PARDS (81). However, Extracorporeal Life Support Organization guidelines are not

clear as to the preferential approach for children with concomitant RV dysfunction (82). Theoretically, RV dysfunction does not immediately preclude VV ECMO given its capability of normalizing pH and $PaCO_2$ and restoring precapillary oxygenation may reduce PVR and improve RV systolic function (83–86). Indeed, reductions in pulmonary arterial and central venous pressures, as well as increases in cardiac index, have been seen with initiation of VV ECMO without adjustments to mechanical ventilation or vasopressor/inotropic support (27, 84, 87–89). VV ECMO also has the benefit of not invading peripheral arteries, which may reduce the risk of bleeding and neurologic complications when compared to VA ECMO deployment through neck vessels (90). On the other hand, VV ECMO does not significantly reduce RV preload and carries the risk of recirculation. Moreover, should RV systolic function continue to deteriorate, VV ECMO can do nothing to provide systemic oxygen delivery and instead results in greater recirculation.

VA ECMO is more commonly selected for children with PARDS in whom VV cannulation is technically not feasible or cardiac failure is also present. VA ECMO through the right internal jugular vein and right common carotid artery diverts systemic venous return from the right atrium to a membrane oxygenator for eventual return to the arterial system distal to the aortic valve. In so doing, preload to the RV and pulmonary vasculature decreases, which would be predicted to reduce RV wall stress, RV afterload, and RV myocardial oxygen demand. It is important to note that carotid return of ECMO blood flow may increase LV afterload and shift myocardial stress from the RV to the LV (91). However, in our experience, most children with severe PARDS requiring ECMO have well-preserved LV function that can withstand the increased afterload. Despite VA ECMO having clear physiological advantages over VV ECMO for children with PARDS and RV dysfunction, neurological risks and overall goals of care must be weighted heavily by all providers in the ECMO cannulation process. Furthermore, it is reasonable, where feasible, to consider transition from VA to VV ECMO in a patient in whom cardiac failure has sufficiently resolved but persistent severe PARDS precludes the sustainability of lung-protective ventilation without ongoing extracorporeal support.

VV ECMO-specific considerations

One of the main goals in using VV ECMO for severe PARDS is to reduce ventilator-induced lung injury while supporting systemic oxygen delivery and carbon dioxide removal. Though optimal ventilator support during VV ECMO is presently unclear, lung protective strategies remain the mainstay of respiratory management during ECMO. During the process of weaning ventilator settings following ECMO deployment, lung de-recruitment is commonplace, potentially worsening RV afterload. Maintaining "adequate PEEP" while on ECMO has been shown to improve survival (92, 93); however, the precise definition of "adequate PEEP" during pediatric ECMO remains unclear. The use of VV ECMO, in particular, may not adequately support the RV in spite of its theoretical benefits of optimizing pulmonary microvascular pH, PCO_2, and PO_2.

If undiagnosed on pre-ECMO evaluation, the development of RV dysfunction is commonly insidious during VV ECMO and may portend cardiopulmonary collapse (94). Therefore, pediatric intensivists must maintain a high index of suspicion for RV dysfunction throughout the ECMO run. Currently there are no guidelines to inform how and when to evaluate for RV dysfunction during VV ECMO. However, as described above, serial evaluation of the clinical exam, circulating biomarkers of end-organ function, and echocardiographic measures of RV performance can be leveraged to identify RV dysfunction early (4, 95, 96). Early identification of RV dysfunction is critical as evidence of RV dilatation and abnormal septal movement post-cannulation are associated with failure to wean from ECMO and increased mortality (94, 97, 98).

It is unknown whether therapies employed prophylactically to reduce RV stress (e.g., iNO, milrinone, prone positioning (27, 99, 100), diuresis (4, 86, 101, 102)) are helpful to mitigate the risk of acquiring RV dysfunction during VV ECMO. Furthermore, when RV dysfunction is uncovered, it is unclear whether conversion to VA ECMO, or the more recently described veno-pulmonary arterial ECMO (103), before RV failure is present can facilitate RV recovery. Once RV failure fully manifests, however, conversion to VA ECMO or implementation of an RV assist device is typically required to salvage the patient as precipitous cardiac arrest is often soon to follow.

We would like to highlight one final consideration in the management of pediatric VV ECMO germane to the patient with known RV dysfunction: use of β-blockers in the management of refractory hypoxemia. Such a clinical scenario is typically reached only when hypoxemia is clinically important (manifested by rising lactate or limitation in other goals of care such as wakefulness), the primary etiology is an isolated elevation in cardiac output, and other potential diagnoses are ruled out or treated. Bunge et al. (104) reported a case series of 33 adults treated with β-blockers for hypoxemia during VV ECMO without incidence of new or worsening RV dysfunction. Guarracino et al. (105) reported their experience in managing 3 adults with sepsis who developed hypoxemia during VV ECMO due to elevated cardiac output. In this small cohort, all patients demonstrated improved systemic oxygenation with an esmolol infusion, though echocardiographic and clinical outcome data were not reported. β-blockers are negative inotropes and thus can promote or exacerbate RV myocardial dysfunction. Therefore, in our estimation, these agents should be prescribed with caution during VV ECMO when RV dysfunction is absent and should be avoided when RV dysfunction is present.

Conclusion

Although a precise definition for RV dysfunction in children has not been settled, it is clear that embarrassment of RV systolic and diastolic function in the setting of PARDS is associated with worse clinical outcomes. PARDS outcomes are usually not dictated by PARDS severity alone and appear to have a greater association with the development of multiorgan failure (2, 106). We postulate that an under-recognized but potentially significant driver of multiorgan failure during PARDS is RV dysfunction and eventual RV failure. The precise incidence of RV dysfunction during PARDS that may better delineate RV dysfunction as a risk factor for PARDS-associated outcomes is currently unknown. We wish to call attention to this insidious pathophysiology during PARDS as its incidence is likely higher than appreciated, and we encourage more a concerted effort by the pediatric critical care research community to help fill this knowledge gap. If RV dysfunction is a significant risk factor for PARDS-associated outcomes as we suspect, then it may behoove pediatric providers to surveil for RV dysfunction sooner and more frequently during the course of severe PARDS. However, additional

knowledge gaps include whether early identification of RV dysfunction in the course of severe PARDS or whether aggressive intervention to prevent or attenuate RV dysfunction during PARDS will improve outcomes.

Author contributions

LW, JL, PP, and RR equally contributed to the conception of the manuscript. LW, LB, AM, PP, JL, and RR substantially contributed to the writing and revision of the manuscript and approve its final draft. All authors contributed to the article and approved the submitted version.

Funding

RR is funded through the National Institutes of Health National Institute of General Medical Sciences grant 5K08 GM144788-02. This grant was used to cover the publication cost for this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Yehya N, Smith L, Thomas NJ, Steffen KM, Zimmerman J, Lee JH, et al. Definition, incidence, and epidemiology of pediatric acute respiratory distress syndrome: from the second Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2023) 24:S87–98. doi: 10.1097/PCC.0000000000003161

2. Dowell JC, Parvathaneni K, Thomas NJ, Khemani RG, Yehya N. Epidemiology of cause of death in pediatric acute respiratory distress syndrome. *Crit Care Med*. (2018) 46:1811–9. doi: 10.1097/CCM.0000000000003371

3. Ganeriwal S, Alves Dos Anjos G, Schleicher M, Hockstein MA, Tonelli AR, Duggal A, et al. Right ventricle-specific therapies in acute respiratory distress syndrome: a scoping review. *Crit Care*. (2023) 27:104. doi: 10.1186/s13054-023-04395-9

4. Petit M, Jullien E, Vieillard-Baron A. Right ventricular function in acute respiratory distress syndrome: impact on outcome, respiratory strategy and use of veno-venous extracorporeal membrane oxygenation. *Front Physiol*. (2021) 12:797252. doi: 10.3389/fphys.2021.797252

5. Brown TN, Brogan TV. Right ventricular dysfunction in patients with acute respiratory distress syndrome receiving venovenous extracorporeal membrane oxygenation. *Front Cardiovasc Med*. (2023) 10:1027300. doi: 10.3389/fcvm.2023.1027300

6. Sato R, Dugar S, Cheungpasitporn W, Schleicher M, Collier P, Vallabhajosyula S, et al. The impact of right ventricular injury on the mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care*. (2021) 25:172. doi: 10.1186/s13054-021-03591-9

7. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. (1994) 149:818–24. doi: 10.1164/ajrccm.149.3.7509706

8. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. (2012) 307:2526–33. doi: 10.1001/jama.2012.5669

9. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. (2012) 38:1573–82. doi: 10.1007/s00134-012-2682-1

10. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2015) 16:428–39. doi: 10.1097/PCC.0000000000000350

11. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. (2000) 342:1301–8. doi: 10.1056/NEJM200005043421801

12. Emeriaud G, Lopez-Fernandez YM, Iyer NP, Bembea MM, Agulnik A, Barbaro RP, et al. Executive summary of the second international guidelines for the diagnosis and Management of Pediatric Acute Respiratory Distress Syndrome (PALICC-2). *Pediatr Crit Care Med*. (2023) 24:143–68. doi: 10.1097/PCC.0000000000003147

13. Fernandez A, Modesto V, Rimensberger PC, Korang SK, Iyer NP, Cheifetz IM, et al. Invasive ventilatory support in patients with pediatric acute respiratory distress syndrome: from the second Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2023) 24:S61–75. doi: 10.1097/PCC.0000000000003159

14. Dahmer MK, Yang G, Zhang M, Quasney MW, Sapru A, Weeks HM, et al. Identification of phenotypes in paediatric patients with acute respiratory distress syndrome: a latent class analysis. *Lancet Respir Med*. (2022) 10:289–97. doi: 10.1016/S2213-2600(21)00382-9

15. Bhalla A, Baudin F, Takeuchi M, Cruces PSecond Pediatric Acute Lung Injury Consensus Conference (PALICC-2) of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Monitoring in pediatric acute respiratory distress syndrome: from the second Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2023) 24:S112–23. doi: 10.1097/PCC.0000000000003163

16. Firpo C, Hoffman JI, Silverman NH. Evaluation of fetal heart dimensions from 12 weeks to term. *Am J Cardiol*. (2001) 87:594–600. doi: 10.1016/s0002-9149(00)01437-5

17. Baum VC, Palmisano BW. The immature heart and anesthesia. *Anesthesiology*. (1997) 87:1529–48. doi: 10.1097/00000542-199712000-00032

18. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation*. (2008) 117:1436–48. doi: 10.1161/CIRCULATIONAHA.107.653576

19. Singh S, White FC, Bloor CM. Myocardial morphometric characteristics in swine. *Circ Res*. (1981) 49:434–41. doi: 10.1161/01.res.49.2.434

20. Yamaguchi S, Harasawa H, Li KS, Zhu D, Santamore WP. Comparative significance in systolic ventricular interaction. *Cardiovasc Res*. (1991) 25:774–83. doi: 10.1093/cvr/25.9.774

21. Woulfe KC, Walker LA. Physiology of the right ventricle across the lifespan. *Front Physiol*. (2021) 12:642284. doi: 10.3389/fphys.2021.642284

22. Brener MI, Masoumi A, Ng VG, Tello K, Bastos MB, Cornwell WK III, et al. Invasive right ventricular pressure-volume analysis: basic principles, clinical applications, and practical recommendations. *Circ Heart Fail*. (2022) 15:e009101. doi: 10.1161/CIRCHEARTFAILURE.121.009101

23. Vieillard-Baron A, Naeije R, Haddad F, Bogaard HJ, Bull TM, Fletcher N, et al. Diagnostic workup, etiologies and management of acute right ventricle failure: a state-of-the-art paper. *Intensive Care Med*. (2018) 44:774–90. doi: 10.1007/s00134-018-5172-2

24. Himebauch AS, Yehya N, Wang Y, Conlon T, Kilbaugh TJ, McGowan FX, et al. Early right ventricular systolic dysfunction and pulmonary hypertension are associated with worse outcomes in pediatric acute respiratory distress syndrome. *Crit Care Med*. (2018) 46:e1055–62. doi: 10.1097/CCM.0000000000003358

25. Himebauch AS, Yehya N, Wang Y, McGowan FX, Mercer-Rosa L. New or persistent right ventricular systolic dysfunction is associated with worse outcomes in pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med*. (2020) 21:e121–8. doi: 10.1097/PCC.0000000000002206

26. Boissier F, Katsahian S, Razazi K, Thille AW, Roche-Campo F, Leon R, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med*. (2013) 39:1725–33. doi: 10.1007/s00134-013-2941-9

27. Mekontso Dessap A, Boissier F, Charron C, Begot E, Repesse X, Legras A, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. *Intensive Care Med*. (2016) 42:862–70. doi: 10.1007/s00134-015-4141-2

28. Auerbach SR, Richmond ME, Lamour JM, Blume ED, Addonizio LJ, Shaddy RE, et al. BNP levels predict outcome in pediatric heart failure patients: post hoc analysis of the pediatric carvedilol trial. *Circ Heart Fail*. (2010) 3:606–11. doi: 10.1161/CIRCHEARTFAILURE.109.906875

29. Chang WT, Shih JY, Hong CS, Lin YW, Chen YC, Ho CH, et al. Right ventricular expression of NT-proBNP adds predictive value to reveal score in patients with pulmonary arterial hypertension. *ESC Heart Fail*. (2021) 8:3082–92. doi: 10.1002/ehf2.13410

30. Cantinotti M. B-type cardiac natriuretic peptides in the neonatal and pediatric intensive care units. *J Pediatr Intensive Care*. (2016) 5:189–97. doi: 10.1055/s-0036-1583543

31. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. (2010) 23:685–713. doi: 10.1016/j.echo.2010.05.010

32. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr*. (2010) 23:465–95. doi: 10.1016/j.echo.2010.03.019

33. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the task force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr*. (2006) 19:1413–30. doi: 10.1016/j.echo.2006.09.001

34. Jone PN, Hinzman J, Wagner BD, Ivy DD, Younoszai A. Right ventricular to left ventricular diameter ratio at end-systole in evaluating outcomes in children with pulmonary hypertension. *J Am Soc Echocardiogr*. (2014) 27:172–8. doi: 10.1016/j.echo.2013.10.014

35. Koestenberger M, Ravekes W. Right ventricular function parameters in the neonatal population. *J Am Soc Echocardiogr*. (2012) 25:243–4. doi: 10.1016/j.echo.2011.12.004

36. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. (2015) 28:1–39.e14. doi: 10.1016/j.echo.2014.10.003

37. Kurath-Koller S, Avian A, Cantinotti M, Burmas A, Grangl G, Schweintzger S, et al. Normal pediatric values of the subcostal tricuspid annular plane systolic excursion (S-TAPSE) and its value in pediatric pulmonary hypertension. *Can J Cardiol*. (2019) 35:899–906. doi: 10.1016/j.cjca.2019.01.019

38. Prada G, Pustavoitau A, Koenig S, Mitchell C, Stainback RF, Diaz-Gomez JL. Focused cardiac ultrasonography for right ventricular size and systolic function. *N Engl J Med*. (2022) 387:e52. doi: 10.1056/NEJMvcm2004089

39. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging*. (2008) 24:691–8. doi: 10.1007/s10554-008-9314-4

40. Giusca S, Dambrauskaite V, Scheurwegs C, D'Hooge J, Claus P, Herbots L, et al. Deformation imaging describes right ventricular function better than longitudinal displacement of the tricuspid ring. *Heart*. (2010) 96:281–8. doi: 10.1136/hrt.2009.171728

41. Lee JZ, Low SW, Pasha AK, Howe CL, Lee KS, Suryanarayana PG. Comparison of tricuspid annular plane systolic excursion with fractional area change for the evaluation of right ventricular systolic function: a meta-analysis. *Open Heart*. (2018) 5:e000667. doi: 10.1136/openhrt-2017-000667

42. Romanowicz J, Ferraro AM, Harrington JK, Sleeper LA, Adar A, Levy PT, et al. Pediatric normal values and *Z* score equations for left and right ventricular strain by two-dimensional speckle-tracking echocardiography derived from a large cohort of healthy children. *J Am Soc Echocardiogr*. (2023) 36:310–23. doi: 10.1016/j.echo.2022.11.006

43. Vieillard-Baron A, Boissier F, Pesenti A. Hemodynamic impact of prone position. Let's protect the lung and its circulation to improve prognosis. *Intensive Care Med*. (2023) 49:692–4. doi: 10.1007/s00134-023-07001-2

44. Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. (2013) 188:1428–33. doi: 10.1164/rccm.201303-0593OC

45. Vieillard-Baron A, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest*. (2007) 132:1440–6. doi: 10.1378/chest.07-1013

46. Coleman RD, Chartan CA, Mourani PM. Intensive care management of right ventricular failure and pulmonary hypertension crises. *Pediatr Pulmonol*. (2021) 56:636–48. doi: 10.1002/ppul.24776

47. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. (2015) 132:2037–99. doi: 10.1161/CIR.0000000000000329

48. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. (2019) 38:879–901. doi: 10.1016/j.healun.2019.06.022

49. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation*. (2018) 137:e578–622. doi: 10.1161/CIR.0000000000000560

50. Siehr SL, Feinstein JA, Yang W, Peng LF, Ogawa MT, Ramamoorthy C. Hemodynamic effects of phenylephrine, vasopressin, and epinephrine in children with pulmonary hypertension: a pilot study. *Pediatr Crit Care Med*. (2016) 17:428–37. doi: 10.1097/PCC.0000000000000716

51. Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V_1-receptor-mediated production of nitric oxide. *Chest*. (1993) 103:1241–5. doi: 10.1378/chest.103.4.1241

52. Banerjee D, Haddad F, Zamanian RT, Nagendran J. Right ventricular failure: a novel era of targeted therapy. *Curr Heart Fail Rep*. (2010) 7:202–11. doi: 10.1007/s11897-010-0031-7

53. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol*. (2001) 38:963–8. doi: 10.1016/s0735-1097(01)01479-6

54. Rimensberger PC, Cheifetz IMPediatric Acute Lung Injury Consensus Conference Group. Ventilatory support in children with pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2015) 16:S51–60. doi: 10.1097/PCC.0000000000000433

55. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. (2013) 368:2159–68. doi: 10.1056/NEJMoa1214103

56. Guérin C, Albert RK, Beitler J, Gattinoni L, Jaber S, Marini JJ, et al. Prone position in ARDS patients: why, when, how and for whom. *Intensive Care Med*. (2020) 46:2385–96. doi: 10.1007/s00134-020-06306-w

57. Papazian L, Munshi L, Guérin C. Prone position in mechanically ventilated patients. *Intensive Care Med*. (2022) 48:1062–5. doi: 10.1007/s00134-022-06731-z

58. Gattinoni L, Busana M, Giosa L, Macrì MM, Quintel M. Prone positioning in acute respiratory distress syndrome. *Semin Respir Crit Care Med*. (2019) 40:94–100. doi: 10.1055/s-0039-1685180

59. Boesing C, Graf PT, Schmitt F, Thiel M, Pelosi P, Rocco PRM, et al. Effects of different positive end-expiratory pressure titration strategies during prone positioning in patients with acute respiratory distress syndrome: a prospective interventional study. *Crit Care*. (2022) 26:82. doi: 10.1186/s13054-022-03956-8

60. Park J, Lee HY, Lee J, Lee SM. Effect of prone positioning on oxygenation and static respiratory system compliance in COVID-19 ARDS vs. non-COVID ARDS. *Respir Res*. (2021) 22:220. doi: 10.1186/s12931-021-01819-4

61. Paternot A, Repessé X, Vieillard-Baron A. Rationale and description of right ventricle-protective ventilation in ARDS. *Respir Care*. (2016) 61:1391–6. doi: 10.4187/respcare.04943

62. Katira BH, Giesinger RE, Engelberts D, Zabini D, Kornecki A, Otulakowski G, et al. Adverse heart-lung interactions in ventilator-induced lung injury. *Am J Respir Crit Care Med*. (2017) 196:1411–21. doi: 10.1164/rccm.201611-2268OC

63. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ. Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. *Intensive Care Med*. (2000) 26:857–69. doi: 10.1007/s001340051274

64. Palmer RM, Ashton DS, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. *Nature*. (1988) 333:664–6. doi: 10.1038/333664a0

65. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. (2016) 2016:CD002787. doi: 10.1002/14651858.CD002787.pub3

66. Domingo LT, Ivy DD, Abman SH, Grenolds AM, MacLean JT, Breaux JA, et al. Novel use of riociguat in infants with severe pulmonary arterial hypertension unable to wean from inhaled nitric oxide. *Front Pediatr*. (2022) 10:1014922. doi: 10.3389/fped.2022.1014922

67. Löllgen H, Drexler H. Use of inotropes in the critical care setting. *Crit Care Med*. (1990) 18:S61–0. doi: 10.1097/00003246-199001002-00011

68. Faritous SZ, Zaree SR, Morshedizad Z, Jalali AH, Mahani SM, Gholampour M. The effect of calcium gluconate administration during cardiopulmonary bypass on hemodynamic variables in infants undergoing open-heart surgery. *Egypt Heart J*. (2022) 74:29. doi: 10.1186/s43044-022-00266-w

69. Elidrissy AT, Munawarah M, Alharbi KM. Hypocalcemic rachitic cardiomyopathy in infants. *J Saudi Heart Assoc*. (2013) 25:25–33. doi: 10.1016/j.jsha.2012.11.003

70. Sanyal D, Raychaudhuri M. Infants with dilated cardiomyopathy and hypocalcemia. *Indian J Endocrinol Metab*. (2013) 17:S221–3. doi: 10.4103/2230-8210.119578

71. Silvetti S, Belletti A, Bianzina S, Momeni M. Effect of Levosimendan treatment in pediatric patients with cardiac dysfunction: an update of a systematic review and meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. (2022) 36:657–64. doi: 10.1053/j.jvca.2021.09.018

72. Gist KM, Mizuno T, Goldstein SL, Vinks A. Retrospective evaluation of milrinone pharmacokinetics in children with kidney injury. *Ther Drug Monit*. (2015) 37:792–6. doi: 10.1097/FTD.0000000000000214

73. Belenkie I, Horne SG, Dani R, Smith ER, Tyberg JV. Effects of aortic constriction during experimental acute right ventricular pressure loading. Further insights into diastolic and systolic ventricular interaction. *Circulation*. (1995) 92:546–54. doi: 10.1161/01.cir.92.3.546

74. Holmes CL, Patel BM, Russell JA, Walley KR. Physiology of vasopressin relevant to management of septic shock. *Chest*. (2001) 120:989–1002. doi: 10.1378/chest.120.3.989

75. Valentine SL, Nadkarni VM, Curley MAPediatric Acute Lung Injury Consensus Conference Group. Nonpulmonary treatments for pediatric acute respiratory distress syndrome: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. (2015) 16:S73–85. doi: 10.1097/PCC.0000000000000435

76. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part ii: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*. (2008) 117:1717–31. doi: 10.1161/CIRCULATIONAHA.107.653584

77. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. *J Am Coll Cardiol*. (2017) 69:236–43. doi: 10.1016/j.jacc.2016.10.047

78. Dell'Italia LJ, Starling MR, Blumhardt R, Lasher JC, O'Rourke RA. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation*. (1985) 72:1327–35. doi: 10.1161/01.cir.72.6.1327

79. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology*. (2001) 96:132–43. doi: 10.1159/000047397

80. Boerrigter G, Burnett JC. Cardiorenal syndrome in decompensated heart failure: prognostic and therapeutic implications. *Curr Heart Fail Rep*. (2004) 1:113–20. doi: 10.1007/s11897-004-0020-9

81. Maratta C, Potera RM, van Leeuwen G, Castillo Moya A, Raman L, Annich GM. Extracorporeal Life Support Organization (ELSO): 2020 Pediatric Respiratory ELSO Guideline. *ASAIO J*. (2020) 66:975–9. doi: 10.1097/MAT.0000000000001223

82. Brown G, Moynihan KM, Deatrick KB, Hoskote A, Sandhu HS, Aganga D, et al. Extracorporeal Life Support Organization (ELSO): guidelines for pediatric cardiac failure. *ASAIO J*. (2021) 67:463–75. doi: 10.1097/MAT.0000000000001431

83. Price LC, McAuley DF, Marino PS, Finney SJ, Griffiths MJ, Wort SJ. Pathophysiology of pulmonary hypertension in acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. (2012) 302:L803–15. doi: 10.1152/ajplung.00355.2011

84. Grant C, Richards JB, Frakes M, Cohen J, Wilcox SR. ECMO and right ventricular failure: review of the literature. *J Intensive Care Med*. (2021) 36:352–60. doi: 10.1177/0885066619900503

85. Lazzeri C, Bonizzoli M, Cianchi G, Batacchi S, Guetti C, Cozzolino M, et al. Right ventricular dysfunction and pre implantation vasopressors in refractory ARDS supported by VV-ECMO. *Heart Lung Circ*. (2018) 27:1483–8. doi: 10.1016/j.hlc.2017.10.011

86. Bunge JJH, Caliskan K, Gommers D, Reis MD. Right ventricular dysfunction during acute respiratory distress syndrome and veno-venous extracorporeal membrane oxygenation. *J Thorac Dis*. (2018) 10:S674–82. doi: 10.21037/jtd.2017.10.75

87. Srivastava MC, Ramani GV, Garcia JP, Griffith BP, Uber PA, Park MH. Veno-venous extracorporeal membrane oxygenation bridging to pharmacotherapy in pulmonary arterial hypertensive crisis. *J Heart Lung Transplant*. (2010) 29:811–3. doi: 10.1016/j.healun.2010.02.005

88. Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Bréchot N, et al. Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. *Intensive Care Med*. (2013) 39:838–46. doi: 10.1007/s00134-012-2785-8

89. Morimont P, Guiot J, Desaive T, Tchana-Sato V, Janssen N, Cagnina A, et al. Veno-venous extracorporeal Co_2 removal improves pulmonary hemodynamics in a porcine ARDS model. *Acta Anaesthesiol Scand*. (2015) 59:448–56. doi: 10.1111/aas.12497

90. Jenks CL, Raman L, Dalton HJ. Pediatric extracorporeal membrane oxygenation. *Crit Care Clin*. (2017) 33:825–41. doi: 10.1016/j.ccc.2017.06.005

91. Cevasco M, Takayama H, Ando M, Garan AR, Naka Y, Takeda K. Left ventricular distension and venting strategies for patients on venoarterial extracorporeal membrane oxygenation. *J Thorac Dis*. (2019) 11:1676–83. doi: 10.21037/jtd.2019.03.29

92. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. (2011) 365:1905–14. doi: 10.1056/NEJMct1103720

93. Schmidt M, Stewart C, Bailey M, Nieszkowska A, Kelly J, Murphy L, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. *Crit Care Med*. (2015) 43:654–64. doi: 10.1097/CCM.0000000000000753

94. Chad T, Yusuff H, Zochios V, Pettenuzzo T, Fan E, Schmidt M, et al. Right ventricular injury increases mortality in patients with acute respiratory distress syndrome on veno-venous extracorporeal membrane oxygenation: a systematic review and meta-analysis. *ASAIO J*. (2023) 69:e14–22. doi: 10.1097/MAT.0000000000001854

95. Douflé G, Roscoe A, Billia F, Fan E. Echocardiography for adult patients supported with extracorporeal membrane oxygenation. *Crit Care*. (2015) 19:326. doi: 10.1186/s13054-015-1042-2

96. Krishnan S, Schmidt GA. Hemodynamic monitoring in the extracorporeal membrane oxygenation patient. *Curr Opin Crit Care*. (2019) 25:285–91. doi: 10.1097/MCC.0000000000000602

97. Lazzeri C, Cianchi G, Bonizzoli M, Batacchi S, Terenzi P, Bernardo P, et al. Right ventricle dilation as a prognostic factor in refractory acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation. *Minerva Anestesiol*. (2016) 82:1043–9.

98. Ortiz F, Brunsvold ME, Bartos JA. Right ventricular dysfunction and mortality after cannulation for venovenous extracorporeal membrane oxygenation. *Crit Care Explor*. (2020) 2:e0268. doi: 10.1097/CCE.0000000000000268

99. Guervilly C, Hraiech S, Gariboldi V, Xeridat F, Dizier S, Toesca R, et al. Prone positioning during veno-venous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome in adults. *Minerva Anestesiol*. (2014) 80:307–13.

100. Rilinger J, Zotzmann V, Bemtgen X, Schumacher C, Biever PM, Duerschmied D, et al. Prone positioning in severe ARDS requiring extracorporeal membrane oxygenation. *Crit Care*. (2020) 24:397. doi: 10.1186/s13054-020-03110-2

101. Mebazaa A, Karpati P, Renaud E, Algotsson L. Acute right ventricular failure-from pathophysiology to new treatments. *Intensive Care Med*. (2004) 30:185–96. doi: 10.1007/s00134-003-2025-3

102. Schmidt M, Bailey M, Kelly J, Hodgson C, Cooper DJ, Scheinkestel C, et al. Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. *Intensive Care Med*. (2014) 40:1256–66. doi: 10.1007/s00134-014-3360-2

103. El Banayosy AM, El Banayosy A, Brewer JM, Mihu MR, Chidester JM, Swant LV, et al. The ProtekDuo for percutaneous V-P and V-VP ECMO in patients with COVID-19 ARDS. *Int J Artif Organs*. (2022) 45:1006–12. doi: 10.1177/03913988221121355

104. Bunge JJH, Diaby S, Valle AL, Bakker J, Gommers D, Vincent JL, et al. Safety and efficacy of beta-blockers to improve oxygenation in patients on veno-venous ECMO. *J Crit Care*. (2019) 53:248–52. doi: 10.1016/j.jcrc.2019.06.024

105. Guarracino F, Zangrillo A, Ruggeri L, Pieri M, Calabro MG, Landoni G, et al. Beta-blockers to optimize peripheral oxygenation during extracorporeal membrane oxygenation: a case series. *J Cardiothorac Vasc Anesth*. (2012) 26:58–63. doi: 10.1053/j.jvca.2011.05.013

106. Beltramo F, Khemani RG. Definition and global epidemiology of pediatric acute respiratory distress syndrome. *Ann Transl Med*. (2019) 7:502. doi: 10.21037/atm.2019.09.31

Glossary

ACP	acute cor pulmonale
ARDS	acute respiratory distress syndrome
BNP	brain-type natriuretic peptide
CRRT	continuous renal replacement therapy
CVP	central venous pressure
ECMO	extracorporeal membrane oxygenation
F_IO_2	fraction of inspired oxygen
FRC	functional residual capacity
iNO	inhaled nitric oxide
LV	left ventricle
PALICC	Pediatric Acute Lung Injury Consensus Conference
PARDS	pediatric acute respiratory distress syndrome
PEEP	positive end-expiratory pressure
PICU	pediatric intensive care unit
PVR	pulmonary vascular resistance
RV	right ventricle
RVEDP	right ventricular end-diastolic pressure
RVEDV	right ventricular end-diastolic volume
SVR	systemic vascular resistance
TAPSE	tricuspid annular plane systolic excursion
TTE	transthoracic echocardiography
VA	venoarterial
V_{TI}	peak velocity of the tricuspid insufficiency jet during systole
VV	venovenous

frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 28 August 2023
DOI 10.3389/fmed.2023.1240321

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Thomas Riva,
University of Bern, Switzerland
Tommaso Mauri,
University of Milan, Italy

*CORRESPONDENCE
Huaiwu He
✉ tjmuhhw@126.com
Yun Long
✉ iculong_yun@163.com

†These authors have contributed equally to this work

RECEIVED 14 June 2023
ACCEPTED 09 August 2023
PUBLISHED 28 August 2023

CITATION
Wang Q, Su L, Jiang J, Wang N, He H and Long Y (2023) Incorporating electrical impedance tomography to transpulmonary pressure-guided PEEP in severe ARDS with pneumothorax and multiple cavitations: a case report.
Front. Med. 10:1240321.
doi: 10.3389/fmed.2023.1240321

Incorporating electrical impedance tomography to transpulmonary pressure-guided PEEP in severe ARDS with pneumothorax and multiple cavitations: a case report

Qianling Wang[1†], Longxiang Su[1†], Jing Jiang[2], Na Wang[1], Huaiwu He[1*] and Yun Long[1*]

[1]Department of Critical Care Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Beijing, China, [2]Department of Critical Care Medicine, Chongqing General Hospital, Chongqing, China

Pneumothorax is a potentially fatal complication in patients with acute respiratory distress syndrome (ARDS), presenting challenges in determining the optimal positive end-expiratory pressure (PEEP) level to prevent atelectasis without exacerbating the pneumothorax. This case report describes the successful application of transpulmonary pressure and electrical impedance tomography (EIT) at the bedside to guide PEEP selection in a patient with ARDS complicated by pneumothorax due to methicillin-resistant *Staphylococcus aureus* infection. By using minimal PEEP to maintain positive end-expiratory transpulmonary pressure and visualizing lung reopening with EIT, the optimal PEEP level was reaffirmed, even if traditionally considered high. The patient's condition improved, and successful weaning from the ventilator was achieved, leading to a transfer out of the intensive care unit.

Clinical trial registration: https://clinicaltrials.gov/show/NCT04081142, identifier NCT04081142.

KEYWORDS

positive end-expiratory pressure, transpulmonary pressure, ARDS, EIT, MRSA pneumonia

Introduction

Pneumothorax is a potentially fatal complication in patients with acute respiratory distress syndrome (ARDS), contributing to high mortality rates. Patients with severe ARDS may necessitate higher positive end-expiratory pressure (PEEP) levels to prevent atelectasis and recruit previously collapsed alveolar units, but this approach becomes contentious when concurrent pneumothorax is present. To address this challenge, adopting an individualized approach to PEEP adjustment, which carefully balances the risk of barotrauma with the need for recruitment, may prove beneficial. Transpulmonary pressure-guided PEEP selection shown to enhance patient outcomes compared to traditional methods (1). Transpulmonary pressure is the pressure difference between airway and pleural pressure, accurately reflects lung stress,

independent of the chest wall. An end-expiratory transpulmonary pressure greater than zero indicates open alveoli throughout the respiratory cycle, whereas a negative value suggests a tendency for alveolar and/or small airway collapse. However, excessively high transpulmonary pressure can lead to alveolar overdistension, exacerbating pneumothorax. In severe ARDS complicated by pneumothorax, precise PEEP adjustment becomes particularly important. While esophageal pressure serves as a surrogate for pleural pressure and offers a relatively less invasive and reliable method for obtaining transpulmonary pressure, factors like mediastinal weight, abdominal pressure, and esophageal balloon positioning may influence measurements (2). Therefore, ensuring the accuracy of transpulmonary pressure-guided PEEP selection through alternative methods is necessary.

Electrical Impedance Tomography (EIT) is a non-invasive, radiation-free bedside imaging technique that provides real-time ventilation monitoring by estimating changes in lung resistivity during respiration, reflecting alterations in intrapulmonary gas volume and conductivity (3). The real-time monitoring provided by EIT offers a valuable solution to address concerns regarding the accuracy of positive PEEP solely determined by esophageal pressure. A recent brief report by Slobod et al. (4) proposed a novel approach to personalize positive PEEP for intubated hypoxemic patients undergoing pressure support ventilation. Their method involves integrating transpulmonary pressure into EIT-based regional compliance calculations. Although promising, further validation is required to ascertain whether this approach indeed improves patient outcomes. In our current case, we propose an alternative approach that integrates EIT-based regional ventilation information into the PEEP adjustment guided by transpulmonary pressure for a patient with ARDS complicated by severe atelectasis and pneumothorax. Our aim is to achieve a more precise and personalized method to address the specific challenges for this patient, potentially leading to improved clinical outcomes.

Case presentation

An 18-year-old female patient was transferred from another hospital to our emergency department with a critical condition of respiratory failure and septic shock, which resulted from the dissemination of methicillin-resistant *Staphylococcus aureus* (MRSA) in her bloodstream, originating from septic arthritis of the left hip. The patient had no history of intravenous drug use or recent hospitalization. During the examination, the patient presented with a heart rate of 112 beats per minute, a temperature of 38.2°C, and a respiratory rate of 22 breaths per minute. Her mean arterial pressure was maintained within the range of 65 to 75 mmHg with the administration of norepinephrine at 0.21 μg/kg/min. The patient had been intubated prior to admission and required mechanical ventilation in pressure support mode, with a pressure support level of 12 cmH2O, PEEP of 6 cmH2O, and an inspired oxygen fraction (FiO2) of 0.4, resulting in a partial pressure of arterial oxygen to inspired oxygen fraction (PaO2/FiO2) ratio of 215 mmHg. A chest computed tomography (CT) scan conducted after her admission revealed multifocal pulmonary opacities and cavitations (Figure 1). Subsequent cardiac ultrasound identified a tricuspid valve vegetation formation measuring 14 mm × 12 mm, along with tricuspid valve leaflet destruction, leading to severe regurgitation, raising concerns for infective endocarditis. The patient underwent tricuspid valve replacement surgery the following day and was immediately transferred to the intensive care unit (ICU).

On DAY 2 after admission to the ICU, a chest X-ray revealed evident exudation and consolidation in both lungs, particularly in the dependent areas. Further ultrasound imaging indicated no significant abnormalities in cardiac function. The patient was under volume-controlled ventilation with a tidal volume (VT) of 5.8 mL/kg predicted bodyweight, a PEEP level of 6 cm H2O, a respiratory rate of 22 breaths/min, and a plateau pressure of 26 cmH2O for lung-protective ventilation. Her PaO2 was 91 mm Hg on an FiO2 of 0.5 (Table 1). Prone position and anti-infective treatment were also administered. On Day 4 after ICU admission, she developed a left-sided tension pneumothorax (Figure 2) and received immediate emergency decompression with a chest drain. On Day 5 after ICU admission, her oxygenation significantly deteriorated (PaO2/FiO2 ratio decreased from 182 to 98). The chest X-ray displayed diffuse exudation in both lungs and significant atelectasis on the right side (Figure 2). Additionally, the left-side thoracic drainage showed ongoing air leaks. In an effort to minimize the risk of alveolar hyperinflation, the tidal volume was further reduced to 3 mL/kg predicted bodyweight to lower the plateau pressure. Additional respiratory parameters of the patient are presented in Table 1. Despite these efforts, the air leaks persisted, and oxygenation did not improve, prompting the need for more precise PEEP settings.

As transpulmonary pressure eliminates the interference of pleural and abdominal pressures, providing a more accurate method for determining the optimal PEEP compared to plateau pressure, and EIT allows real-time bedside visualization of the effects of different PEEP levels determined by transpulmonary pressure on ventilation. Therefore, we employed esophageal pressure combined with EIT to select the optimal PEEP, aiming to avoid lung injury caused by alveolar overdistension while preventing atelectasis and recruiting previously collapsed alveolar units. She remained deeply sedated, and a continuous infusion of neuromuscular blocking agents was administered to ensure controlled ventilation and prevent spontaneous breathing efforts. The protocol for esophageal pressure measurement followed the methods described in our previous study (5). Setting the PEEP at 12 cmH2O resulted in an end-expiratory esophageal pressure of 16.9 cmH2O, corresponding to an end-expiratory transpulmonary pressure of −4.9 cmH2O. However, when the PEEP was increased to 15 cmH2O, the end-expiratory esophageal pressure reduced to 15.7 cmH2O, and the end-expiratory transpulmonary pressure became positive, reaching 0.7 cmH2O. Therefore, a PEEP of 15 cmH2O was considered the minimum PEEP required to effectively maintain alveolar recruitment and prevent atelectasis.

Remarkably, within 10 min of increasing the PEEP from 12 to 15 cmH2O (Figure 2), significant recruitment in the right lung was observed without an increase in the volume of air leakage. Ventilation distribution was closely monitored for the following 6 h to ensure no further pneumothorax occurred. Concurrently, end-expiratory lung impedance increased during the EIT measurement period, confirming the positive response to the adjusted PEEP. For EIT measurements, an EIT electrode belt with 16 electrodes was positioned around the thorax in the fourth to fifth intercostal space, with one reference electrode placed on the patient's abdomen using the PulmoVista 500 system by Dräger Medical, Lübeck, Germany.

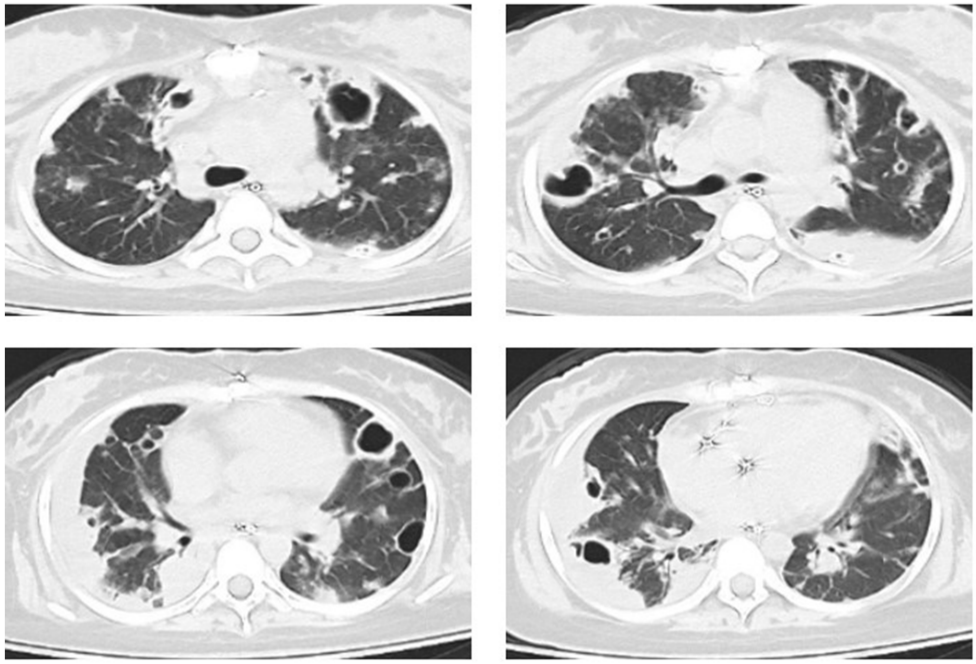


FIGURE 1
CT scan showed multiple cavitary infiltrates in both lungs on admission.

TABLE 1 Respiratory parameters of the patient during ICU admission.

Date	DAY 2	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11
Tidal volume (ml/kg predicted bodyweight)	5.8	3	3	3.5	4	4	6	6
Respiratory rate (breaths per minute)	22	34	32	30	28	28	18	18
PaCO2 (mmHg)	39	58	56	49	48	45	42	40
Plateau pressure (cmH2O)	24	25	25	25	24	23	20	20
PEEP (cmH2O)	6	15	15	12	12	12	9	9
End-expiratory transpulmonary (cmH2O)	NA	0.7	0.9	1.0	0.9	0.9	0.6	0.8
Ventilatory mode	VC	VC	VC	VC	VC	VC	VC	VC
PaO2/FiO2	182	98	115	122	167	191	216	230

PaCO2 denotes arterial partial pressure of carbon dioxide; PEEP denotes positive end-expiratory pressure; PaO2/FiO2 denotes partial pressure of arterial oxygen to inspired oxygen fraction; DAY 2 denotes the DAY 2 of ICU admission; VC denotes volume control; NA denotes not available.

From day 6 of ICU admission, no additional air leaks were recorded. Arterial oxygenation improved, and the chest X-ray showed a reduction in atelectasis and exudation. On day 11 of ICU admission, the thoracic drainage tube was safely removed, and the ventilator mode was transitioned from volume-controlled ventilation to pressure-supported ventilation. Gradually, her oxygenation improved, and a lung CT on day 19 of ICU admission revealed significant absorption of bilateral pulmonary infiltrates and cavitation, with no signs of pneumothorax. The patient was successfully extubated the following day and subsequently transitioned to high-flow nasal oxygen therapy. Eventually, the patient was discharged from the ICU on the 25th day of admission.

Discussion

Severe ARDS caused by MRSA bloodstream infection, complicated by multiple cavitation and pneumothorax, is associated with a very high rate of morbidity and mortality. In this case, we achieved more accurate PEEP in a mechanically ventilated patient

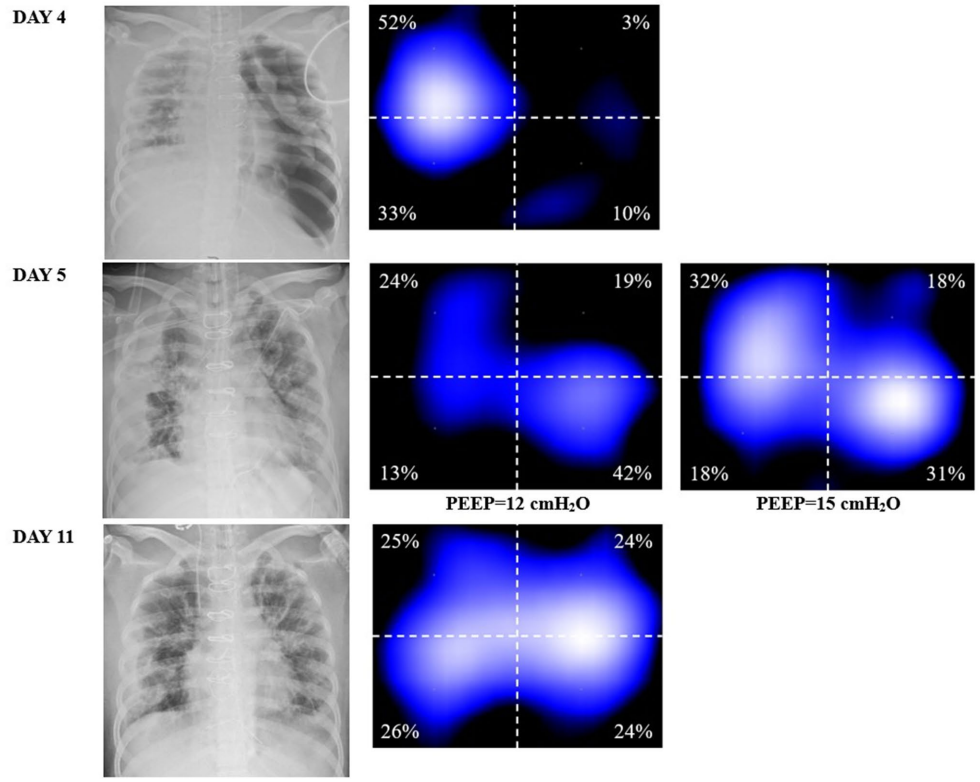


FIGURE 2
DAY 4, the chest X-ray indicating tension pneumothorax and the corresponding EIT ventilation image, showing a significant decrease in ventilation in the left lung. DAY 5, chest X-ray (at a PEEP of 6 cmH2O) shows left lung reopening after transthoracic drainage, but right lung atelectasis. At a PEEP of 15 cmH2O, the right lung was better ventilated compared to that at 12 cmH2O (well ventilated regions in light blue in EIT). DAY 11, improvement in exudation and atelectasis, the left side chest drain has been removed, and the homogeneity of ventilation in both lungs has been improved compared to the previous status.

using a combination of transpulmonary pressure and EIT. As a result, the patient gradually recovered, was successfully weaned from the ventilator, and transferred out of the ICU.

PEEP plays a crucial role in preventing atelectasis and reducing atelectrauma caused by periodic recruitment and decruitment. In cases of severe ARDS, higher levels of PEEP may be required to achieve the treatment targets (6). However, in patients complicated by pneumothorax and cavitation, setting higher PEEP levels can be a dilemma as it may induce or worsen pneumothorax in such individuals (7, 8). Previous studies have analyzed the association between airway pressure and barotrauma risk in patients with acute lung injury (ALI)/ARDS. Eisner et al. (9) retrospectively analyzed a cohort of 718 patients without baseline barotrauma and found that higher PEEP was associated with an increased risk of early barotrauma. Similarly, a study in patients with ARDS due to COVID-19 also reported similar results (10). The underlying reason could be that excessive PEEP may lead to an increased transpulmonary pressure, potentially causing barotrauma. However, it is crucial to recognize that higher PEEP levels is not an absolute contraindication for pneumothorax, as this does not consistently signify excessive transpulmonary pressure, which is the primary determinant contributing to alveolar overdistension. A systematic review and meta-analysis have suggested that the occurrence of pneumothorax is not significantly related to high PEEP (11). Therefore, in severe ARDS with pneumothorax and multiple cavitations, achieving an appropriate PEEP setting becomes challenging due to the need to carefully balance alveolar recruitment and overdistension.

If we have to make a choice between low PEEP and high PEEP for this patient, we must carefully consider the benefits and potential harms of each approach. High PEEP offers the advantage of avoiding atelectrauma, which is caused by alveolar collapse associated with low end-expiratory lung volumes and injuries resulting from mechanical forces involved in repeated opening and closing of small bronchioles and alveoli during tidal ventilation (12). By maintaining alveolar opening throughout the respiratory cycle, high PEEP increases functional residual capacity and lung compliance, reducing the risk of atelectrauma. However, the high PEEP carries the disadvantage of potentially inducing barotrauma due to increased transpulmonary pressure and alveolar overdistension, which could worsen pneumothorax – a concerning complication in patients with pneumothorax and multiple cavitations. The advantages and disadvantages of Low PEEP are opposite to those of High PEEP. On the DAY 5 of ICU admission, the patient experienced a significant exacerbation of oxygenation due to the emergence of severe atelectasis, alongside existing pneumothorax and multiple cavitations. Therefore, we believe that the optimal PEEP for this patient is the minimum level required to keep the alveoli open even at end-expiration. During controlled ventilation, transpulmonary pressure is calculated as the difference between PEEP (a surrogate for airway pressure) and esophageal pressure (a surrogate for pleural pressure) at end-expiration (13). A transpulmonary pressure greater than zero indicates that the

alveoli remain open throughout the respiratory cycle (14). A previous study suggested that mortality might be reduced when PEEP titration achieves end-expiratory transpulmonary pressure near 0 cm H2O in patients with ALI or ARDS (1). In this case, a PEEP of no less than 15 was required to achieve a positive end-expiratory transpulmonary pressure, which may be considered relatively high according to traditional standards.

Given the concerns about the high PEEP and the accuracy of the transpulmonary pressure measurement, we employ a more intuitive way to prove the reliability of this PEEP. EIT is a non-invasive and radiation-free clinical imaging tool used to monitor ventilation distribution in real-time and at the bedside (15). It provides continuous image monitoring, helping optimize mechanical ventilation settings, and detect complications such as decruitment and pneumothorax. EIT's ability to detect even small pneumothoraces of 20 mL in real-time has been demonstrated previously (16). With the help of EIT, we confirmed a substantial improvement in ventilation distribution on the right lung after increasing PEEP from 12 to 15 cmH2O. The images showed a more homogeneous distribution between the lung areas. This evidence allowed us to titrate mechanical ventilation parameters more accurately and individually, overcoming concerns associated with the use of 'high PEEP' in ARDS complicated by pneumothorax.

Clinical practice can be challenging for clinicians, especially when dealing with non-standard patients and conflicting treatment options, as often seen in critically ill patients. The choice of the best option in such situations is crucial. In severe ARDS, a single approach to determining the optimal PEEP may have limitations, and no single method has been shown to improve clinical outcomes significantly compared to others (12). Combining different techniques, such as EIT and esophageal pressure, to determine the optimal PEEP more accurately could lead to improved clinical outcomes or provide solutions to clinical dilemmas.

In conclusion, pneumothorax is a life-threatening complication of severe ARDS, and individualizing PEEP is crucial to achieve alveolar recruitment while avoiding alveolar overdistension or exacerbation of pneumothorax. We presented a novel idea of incorporating regional ventilation information provided by EIT as a safety measure for severe ARDS complicated with pneumothorax and multiple cavitations after transpulmonary pressure-guided PEEP selection. In the complex clinical settings of mechanical ventilation, a more precise approach could yield benefits by involving the combination of various techniques rather than relying solely on a single approach in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QW and HH prepared the final copy of the manuscript and EIT images. LS, JJ, and NW performed the EIT examination. QW obtained patient's consent. HH and YL edited and revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National High-Level Hospital Clinical Research Funding (2022-PUMCH-D-005, 2022-PUMCH-B-115).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sarge T, Baedorf-Kassis E, Banner-Goodspeed V, Novack V, Loring SH, Gong MN, et al. Effect of esophageal pressure-guided positive end-expiratory pressure on survival from acute respiratory distress syndrome: a risk-based and mechanistic reanalysis of the epvent-2 trial. *Am J Respir Crit Care Med*. (2021) 204:1153–63. doi: 10.1164/rccm.202009-3539OC

2. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, et al. Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med*. (2016) 42:1360–73. doi: 10.1007/s00134-016-4400-x

3. He H, Chi Y, Yang Y, Yuan S, Long Y, Zhao P, et al. Early individualized positive end-expiratory pressure guided by electrical impedance tomography in acute respiratory distress syndrome: a randomized controlled clinical trial. *Crit Care*. (2021) 25:230. doi: 10.1186/s13054-021-03645-y

4. Slobod D, Leali M, Spinelli E, Grieco DL, Spadaro S, Mauri T. Integrating electrical impedance tomography and transpulmonary pressure monitoring to personalize peep in hypoxemic patients undergoing pressure support ventilation. *Crit Care*. (2022) 26:314. doi: 10.1186/s13054-022-04198-4

5. Jiang J, Su L, Cheng W, Wang C, Rui X, Tang B, et al. The calibration of esophageal pressure by proper esophageal balloon filling volume: a clinical study. *Front Med (Lausanne)*. (2022) 9:986982. doi: 10.3389/fmed.2022.986982

6. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med*. (2017) 377:562–72. doi: 10.1056/NEJMra1608077

7. Ioannidis G, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, Lampaki S, et al. Barotrauma and pneumothorax. *J Thorac Dis*. (2015) 7:S38–43. doi: 10.3978/j.issn.2072-1439.2015.01.31

8. Woodside KJ, Van Sonnenberg E, Chon KS, Loran DB, Tocino IM, Zwischenberger JB. Pneumothorax in patients with acute respiratory distress syndrome: pathophysiology, detection, and treatment. *J Intensive Care Med*. (2003) 18:9–20. doi: 10.1177/0885066602239120

9. Eisner MD, Thompson BT, Schoenfeld D, Anzueto A, Matthay MA. Airway pressures and early barotrauma in patients with acute lung injury and acute respiratory

distress syndrome. *Am J Respir Crit Care Med*. (2002) 165:978–82. doi: 10.1164/ajrccm.165.7.2109059

10. Guven BB, Erturk T, Kompe O, Ersoy A. Serious complications in covid-19 ards cases: pneumothorax, pneumomediastinum, subcutaneous emphysema and haemothorax. *Epidemiol Infect*. (2021) 149:e137. doi: 10.1017/S0950268821001291

11. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. (2010) 303:865–73. doi: 10.1001/jama.2010.218

12. Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ards. Setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. (2017) 195:1429–38. doi: 10.1164/rccm.201610-2035CI

13. Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. *Am J Respir Crit Care Med*. (2016) 194:1452–7. doi: 10.1164/rccm.201512-2448CP

14. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. (2008) 359:2095–104. doi: 10.1056/NEJMoa0708638

15. Bachmann MC, Morais C, Bugedo G, Bruhn A, Morales A, Borges JB, et al. Electrical impedance tomography in acute respiratory distress syndrome. *Crit Care*. (2018) 22:263. doi: 10.1186/s13054-018-2195-6

16. Costa EL, Chaves CN, Gomes S, Beraldo MA, Volpe MS, Tucci MR, et al. Real-time detection of pneumothorax using electrical impedance tomography. *Crit Care Med*. (2008) 36:1230–8. doi: 10.1097/CCM.0b013e31816a0380

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 29 August 2023
DOI 10.3389/fmed.2023.1233609

OPEN ACCESS

EDITED BY
Antonio M. Esquinas,
Hospital General Universitario Morales Meseguer, Spain

REVIEWED BY
Adam L. Balogh,
University of Szeged, Hungary
Tobias Becher,
University Medical Center Schleswig-Holstein, Germany

*CORRESPONDENCE
Thomas Riedel
✉ thomas.riedel@insel.ch

RECEIVED 05 June 2023
ACCEPTED 31 July 2023
PUBLISHED 29 August 2023

CITATION
Braun M, Ruscher L, Fuchs A, Kämpfer M, Huber M, Luedi MM, Riva T, Vogt A and Riedel T (2023) Atelectasis in obese patients undergoing laparoscopic bariatric surgery are not increased upon discharge from Post Anesthesia Care Unit. *Front. Med.* 10:1233609. doi: 10.3389/fmed.2023.1233609

Atelectasis in obese patients undergoing laparoscopic bariatric surgery are not increased upon discharge from Post Anesthesia Care Unit

Matthias Braun[1], Lea Ruscher[2], Alexander Fuchs[2,3], Martina Kämpfer[2], Markus Huber[2], Markus M. Luedi[2], Thomas Riva[2], Andreas Vogt[2] and Thomas Riedel[4]*

[1]Department of Anaesthesiology, Lindenhof Hospital, Bern, Switzerland, [2]Department of Anaesthesiology and Pain Medicine, Bern University Hospital, Inselspital, University of Bern, Bern, Switzerland, [3]Unit for Research in Anaesthesia, IRCCS Istituto Giannina Gaslini, Genoa, Italy, [4]Division of Paediatric Intensive Care Medicine, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Background: Obese patients frequently develop pulmonary atelectasis upon general anesthesia. The risk is increased during laparoscopic surgery. This prospective, observational single-center study evaluated atelectasis dynamics using Electric Impedance Tomography (EIT) in patients undergoing laparoscopic bariatric surgery.

Methods: We included adult patients with ASA physical status I–IV and a BMI of ≥40. Exclusion criteria were known severe pulmonary hypertension, home oxygen therapy, heart failure, and recent pulmonary infections. The primary outcome was the proportion of poorly ventilated lung regions (low tidal variation areas) and the global inhomogeneity (GI) index assessed by EIT before discharge from the Post Anesthesia Care Unit compared to these same measures prior to initiation of anesthesia.

Results: The median (IQR) proportion of low tidal variation areas at the different analysis points were T1 10.8% [3.6–15.1%] and T5 10.3% [2.6–18.9%], and the mean difference was −0.7% (95% CI: −5.8% −4.5%), i.e., lower than the predefined non-inferiority margin of 5% ($p = 0.022$). There were no changes at the four additional time points compared to T1 or postoperative pulmonary complications during the 14 days following the procedure.

Conclusion: We found that obese patients undergoing laparoscopic bariatric surgery do not leave the Post Anesthesia Care Unit with increased low tidal variation areas compared to the preoperative period.

KEYWORDS

adipositas, general anesthesia, laparoscopic surgery, bariatric (weight loss) surgery, mechanical ventilation

Introduction

Postoperative pulmonary complications (PPC) increase morbidity, mortality, length of hospital stay, and costs (1–3). A frequent PPC is the formation of atelectasis, which is increased under general anesthesia, supine position, and controlled ventilation. Increased intra-abdominal pressure in laparoscopic surgery also increases the risk of atelectasis

formation (1). Obese patients are more affected by developing postoperative pulmonary complications and atelectasis under general anesthesia (1, 4, 5). They tend to take longer to reopen atelectasis than non-obese patients and experience poor ventilation over a significant period of time (6, 7).

Protective ventilatory strategies using lower tidal volumes, increased positive end-expiratory pressure (PEEP), and recruitment maneuvers (8, 9) have been shown to reduce PPC, including atelectasis, and to result in a shorter postoperative anesthesia care unit (PACU) stay (1, 10). The combination of recruitment maneuvers and PEEP could lead to transiently improved oxygenation (4). Nevertheless, obese patients often receive high tidal ventilation with low PEEP and rarely receive recruitment maneuvers (11).

Intraoperative alveolar recruitment followed by PEEP of 10 cm H_2O was associated with less atelectasis assessed with computer tomography compared to no PEEP or PEEP of 5 cm H_2O in obese patients undergoing laparoscopic bariatric surgery (1).

In a cohort of obese patients, 10 cm H_2O PEEP improved oxygenation but did not reverse the formation of atelectasis intraoperatively (12). Individually titrated PEEP by electrical impedance tomography (EIT) and recruitment maneuvers lead to pulmonary conditions being on a level comparable to preoperative conditions in obese patients. Nevertheless, atelectasis was reformed before discharge from the PACU, and end-expiratory lung volume was lower than the preoperative value (13). On the contrary, in small children, a population physiologically similar to obese patients, general anesthesia maintaining spontaneous ventilation homogeneity was fully resolved at discharge from the PACU (14).

Actual bariatric surgery numbers are rising fast, and more obese patients receive surgery. With the persisting trend for ambulatory or short-stay surgery, it is essential to know which pulmonary condition patients can be discharged early from PACU and the hospital to avoid costly hospital stays and readmission. However, the potential benefits of 10 cm H_20 PEEP and repeated recruitment maneuvers to prevent perioperative atelectasis in this cohort are unclear. We aimed to investigate perioperatively atelectasis formation in obese patients scheduled for laparoscopic bariatric surgery from the preoperative phase until discharge from the PACU and the hospital, using electrical impedance tomography: a technique that can detect minimally ventilated lung regions rapidly, continuously, and without harmful radiation or other physical harm to the patient.

Materials and methods

The study was approved by the local ethics committee of the Canton of Bern (BASEC 2021-01473) and prospectively registered with ClinicalTrials.gov (NCT05187039). Written informed consent was obtained from each participant.

Study design and patients

We included 30 patients in this single-center prospective observational trial conducted at the Department of Anesthesiology and Pain Medicine at Bern University Hospital, Switzerland, from 01 November 2021 to 30 September 2022.

The inclusion criteria were patients over 18 years of age who provided written informed consent and were scheduled for laparoscopic bariatric surgery with a body mass index (BMI) of $\geq$40 and an ASA physical status of I to IV.

Exclusion criteria were known severe pulmonary hypertension, need for home oxygen therapy, known heart failure, and suspected or known recent pulmonary infections. Eligible patients were screened from the preadmission clinic or operating room lists and recruited in the preadmission clinic or the preadmission area.

All methods were performed in accordance with the relevant guidelines and regulations and this manuscript follows the applicable STROBE guidelines (see Figure 1).

Anesthesia and measurement

The patients did not receive pharmacological premedication. Participating patients were prepared for general anesthesia according to the departmental standard operating procedure with SpO_2, electrocardiogram, non-invasive blood pressure, quantitative neuromuscular monitoring (TOF-Watch, Organon Ltd, Dublin, Ireland), and an intravenous line. Anesthesia was induced with Propofol 2–3 mg/kg (predicted body weight), Fentanyl 2 mcg/kg (predicted body weight), and Succinylcholine 1 mg/kg (total body weight) or Rocuronium 0.9 mg/kg (predicted body weight) if Succinylcholine was contraindicated. The patients were induced with a modified rapid sequence intubation technique and were all ventilated after apnea started with bag-mask ventilation and a ventilatory pression not exceeding 10 mm Hg. Male participants were intubated with a cuffed tracheal tube size of 8.0 and female participants with 7.0. Successful tracheal intubation was confirmed with waveform capnography. Anesthesia was maintained by volatile anesthetics (MAC 0.75) and Fentanyl guided by an electroencephalogram (Narcotrend, Hannover, Germany). Rocuronium boluses were given to support a "train of four" ratio of 0 of 4. Co-analgesics (i.e., Dexmedetomidine and Ketamine) and other medications (e.g., Dexamethasone and Ondansetron) were given according to standard operating procedures in our bariatric surgery clinic. After intubation and before surgical incision, regional anesthesia (subcostal transversus abdominis plane block) was set using ultrasound guidance with 75 mg Ropivacaine 0.375% per side. While the patient was prepared for the surgical procedure and sterile drapes were applied, a standard recruitment maneuver (40 cmH_2O for 10 s, repeated twice) was performed before surgical disinfection. Patients were ventilated with an anesthetic respirator (Primus, Draeger, Germany) in a volume-controlled mode with a tidal volume of 6–8 ml/kg ideal body weight in a frequency of 12–16/min, the PEEP level set at 10 cm H_2O, and a fraction of inspired oxygen (FiO_2) at 0.6. According to the capnography reading, the frequency was adjusted during pneumoperitoneum to maintain an end-tidal CO_2 between 30 and 40 mmHg according to the usual standards of care. Anesthesia was usually induced in a ramped position by arranging a ramping cushion under the patient's upper body and head. Patients are positioned in an anti-Trendelenburg position shortly before the surgery started.

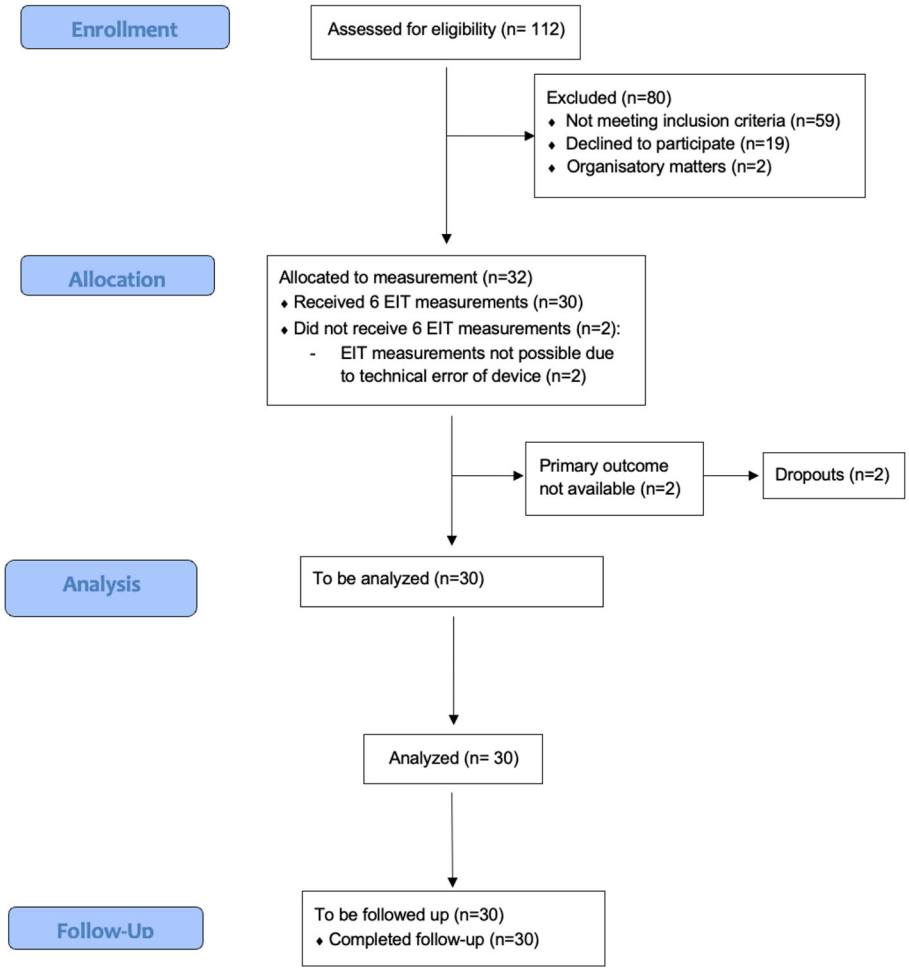


FIGURE 1
STROBE diagram.

Before extubation, neuromuscular blocking was antagonized in all patients with 200 mg of Sugammadex to achieve a "train of four" ratio of >90%. During the emergence of anesthesia, the patients were ventilated in pressure support mode with a PEEP of 5 mm Hg and pressure support of 5–8 mm Hg. In PACU, all patients received conventional oxygen therapy with flows 4–6 l/min.

Thoracic electrical impedance tomography measurements (Pulmovista, Dräger, Germany) were performed at the following time points:

- T1: before induction of the anesthesia.
- T2: after intubation and recruitment maneuvers, before the surgical procedure.
- T3: after the surgical procedure, before extubation.
- T4: after extubation, before transfer to the PACU.
- T5: after 2 h of surveillance, before discharge from the PACU.
- T6: before discharge to home.

A loose-fitting belt with 16 evenly spaced electrodes was placed around each patient's chest between the 4 and 6th intercostal space in a thoracic median plane as soon as the patient arrived in the operation theater. The belt was removed after the T5-measurement before the patient was discharged from the PACU and transferred to the regular surgical ward. To ensure that the belt was reapplied in the same position before the T6-measurement, the upper and lower edges of the belt and the placement of the electrodes on the chest were labeled with a marker, which was renewed daily by ward nurses. Each measurement lasted 1 min. The EIT images were reconstructed based on the Graz consensus reconstruction algorithm for EIT (GREIT) using the torso mesh function based on generic CT scans (15, 16). No additional regions of interest were applied for any of the analyses. The following EIT parameters were calculated for each time point: percentage in low tidal variation areas (defined as areas within the thorax that exhibit <10% of the maximum detected tidal impedance change) and the global inhomogeneity (GI) index, a measure of ventilation inhomogeneity (17). All analyses used a custom code (MATLAB R2021a; The MathWorks Inc., Natick, MA, USA) (18–20). We performed a telephone follow-up 14 days after the surgery to inquire about postoperative pulmonary complications or the need for re-hospitalization.

Postoperative pulmonary complications were defined as respiratory failure, acute respiratory distress syndrome requiring reintubation, respiratory support or rehospitalization, bronchospasm, and new pulmonary infiltrates.

Primary and secondary outcomes

The primary outcome was the percentage of low tidal variation areas derived from EIT before the discharge from PACU (T5) compared to the measurement before induction (T1).

This analysis is based on the analysis of Ukere et al. with the difference that we do not use anatomically defined lung regions (21). This has the advantage that no minimally ventilated lung regions are *a-priori* excluded from the analysis. The disadvantage is that areas outside the patient's lungs can also be included, which overestimates the low tidal variation areas. Secondary outcomes included changes from baseline (T1) in low tidal variation areas, ventilation inhomogeneity at all other time points (T2, T3, T4, and T6), and postoperative pulmonary complications until 14 days after the procedure.

Statistical analysis

Currently, there are no data regarding the extent of atelectasis formation in patients undergoing bariatric surgery at the time of discharge from PACU. We hypothesized that the absolute percentage of low tidal variation areas at PACU discharge is at most 5% higher than before the operation, based on a small pilot study ($N = 5$), where the percentage of low tidal variation areas was measured before intubation and after PACU discharge. To investigate this hypothesis, we chose a non-inferiority design with a corresponding non-inferiority margin of 5% (absolute percentage). Formally, our hypothesis for the percentages of low tidal variation areas before the operation (π_{pre}) and after PACU discharge (π_{post}) can be stated as:

- Null hypothesis (H_0): $\pi_{post} > \pi_{pre} + \Delta$,
- Alternative hypothesis (H_1): $\pi_{post} \leq \pi_{pre} + \Delta$,

where Δ refers to the non-inferiority margin of 5%.

Using the observed values of the pilot study ($N = 5$), we performed a simulation study to estimate the required sample size. Given the repeated measure design of the study and the continuous, bounded primary outcome (percentage of low tidal variation areas), the simulation was based on a generalized linear mixed model (GLMM) with a beta distribution for the outcome, resulting in an estimate of $N = 20$. So far, there are only data for the functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen (22). This previous study set the sample size at 23 participants in each group. A similar study in adults set the sample size at 20 participants per group (23). Accounting for the pilot study's small size and possible dropouts, we envisaged a sample size of $N = 30$ patients. The initial sample size estimate could not be reproduced and a *post-hoc* validity check resulted in a power of 94.2% to declare non-inferiority (significance level of $\alpha = 0.025$ and $\Delta = 5\%$) for $N = 30$ patients.

The primary outcome [change in the percentage of low tidal variation areas after PACU discharge (T5) relative to the percentage of low tidal variation areas before the operation (T1)] was analyzed in a regression framework: GLMM with a beta distribution was used to estimate the primary outcome. The GLMM was used to estimate a 95% confidence interval (CI) of the change in the percentage of low tidal variation areas, and the lower boundary of the CI will be compared to the non-inferiority margin. Non-inferiority—and the rejection of the Null hypothesis—will be declared if the lower boundary of 95% CI is smaller than the pre-defined non-inferiority margin of Δ (5%). The GLMM also allows controlling for covariates that could affect the perioperative reduction of lung impedance. As covariates, we include age and anesthesia time.

A secondary and explorative analysis examined *post-hoc* comparisons of the change from baseline (T1) in the percentage of low tidal variation areas and ventilation inhomogeneity at different time points (T2, T3, T4, and T6). For the secondary analyses, a Friedman Test was performed, and the corresponding contrasts were adjusted for multiple comparisons using the Conover method (24).

A $p < 0.05$ indicated statistical significance, and all analyses were performed in StatsDirect (StatsDirect Ltd, Wirral, United Kingdom) and R (25).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Results

We recruited 32 patients, of which 30, for whom we obtained all measurements and follow-up, were analyzed (Figure 1). Due to a technical error of the EIT device, measurements could not be performed in two patients. Table 1 summarizes the baseline characteristics of the patients. The median age was 43 [32.5–48.0], and 19 patients (63.3%) were female. Median BMI was 45.6 [42.4–49.7] $kg.m^{-2}$, and most patients had an ASA physical status of III (83.3%). Twenty-four patients obtained a laparoscopic gastric sleeve, while six obtained a laparoscopic gastric bypass. The mean duration of the surgical procedure was 64.0 min [50.5–80.5], and the average time of capnoperitoneum was 50.5 min [35.0–69.5]. The ventilation strategy resulted in mean (SD) plateau pressures of 24.2 (2.3) mbar, with tidal volumes of 517 (75.5) ml resulting in a respiratory system compliance of 37.9 (4.8) ml/mbar. Table 2 summarizes the perioperative anesthetic management.

Primary outcome

The mean difference in the percentage of low tidal variation areas between T5 and T1 was −0.7% (95% CI: −5.8% −4.5%), i.e., less than the predefined non-inferiority

10.3389/fmed.2023.1233609

TABLE 1 Baseline characteristics.

	All patients $N = 30$
Age (years) [median (IQR)]	43.0 [32.5; 48.0]
Gender (female) [*n* (%)]:	19 (63.3%)
Height (cm) [median (IQR)]	172 [160; 176]
Weight (kg) [median (IQR)]	130 [116; 146]
Body mass index (BMI; $kg.m^{-2}$) [median (IQR)]	45.6 [42.4; 49.7]
ASA physical status [*n* (%)]:	
II	4 (13.3%)
III	25 (83.3%)
IV	1 (3.33%)

IQR, Interquartile range.

TABLE 2 Perioperative anesthetic management.

Induction of anesthesia	
Propofol [*n* (%)]:	30/30 (100%)
Total Propofol (mg) [median (IQR)]	200 [200; 240]
Succinylcholine	23/30 (76.7%)
Total Succinylcholine (mg) [median (IQR)]	150 [138; 195]
Rocuronium	13/30 (43.3%)
Total Rocuronium (mg) [median (IQR)]	70.0 [30.0; 90.0]
Fentanyl	30/30 (100%)
Total Fentanyl (mcg) [median (IQR)]	200 [150; 200]
Remifentanil	1/30 (3.3%)
Total Remifentanil (mcg)	150
Ketamine	4/30 (13.3%)
Ketamine 20 mg [*n* (%)]:	1/4 (25.0%)
Ketamine 30 mg [*n* (%)]:	1/4 (25.0%)
Ketamine 50 mg [*n* (%)]:	2/4 (50.0%)
Regional anesthesia with Ropivacaine [*n* (%)]:	30/30 (100%)
Total Ropivacaine 0.375% (mg) [median (IQR)]	150 [150; 150]
Maintenance of anesthesia	
Sevoflurane [*n* (%)]:	28/30 (93.3%)
Desflurane [*n* (%)]:	2/30 (6.7%)
MAC [median (IQR)]	0.80 [0.70; 0.80]
Dexmedetomidine	29/30 (96.7%)
Total Dexmedetomidine (mcg) [median (IQR)]	85.3 [64.0; 94.0]
Ketamine	19/30 (63.3%)
Total Ketamine (mg) [median (IQR)]	35.0 [30.0; 40.0]
Rocuronium	29/30 (96.7%)
Total Rocuronium (mg) [median (IQR)]	60.0 [40.0; 70.0]
Fentanyl	27/30 (90.0%)
Total Fentanyl (mcg) [median (IQR)]	150 [100; 225]
Remifentanil	6/30 (20.0%)
Total Remifentanil (mcg) [median (IQR)]	455 [302; 634] [$N = 3$]
Procedure-related durations and oxygen desaturation	
Duration of anesthesia (min) [median (IQR)]	149 [123; 168]
Duration of surgery (min) [median (IQR)]	64.0 [50.5; 80.5]
Duration of capnoperitoneum (min) [median (IQR)]	50.5 [35.0; 69.5]
Type of laparoscopic bariatric surgery:	
Gastric sleeve [*n* (%)]:	24/30 (80.0%)
Gastric bypass [*n* (%)]:	6/30 (20.0%)
Desaturation ($SpO_2 < 90\%$) [*n* (%)]:	6/30 (20.0%)

margin of 5%. The *p*-value for non-inferiority was $p = 0.022$. Therefore, we can assume non-inferiority at T5 compared to T1 (Figure 2).

Secondary outcomes

The median (IQR) proportions of low tidal variation areas at the different time points were T1 10.8% [3.6–15.1%], T2 8.5% [6.2–15.6%], T3 4.7% [2.0–8.3%], T4 7.9% [5.0–17.2%], T5 10.3% [2.6–18.9%], and T6 14.5% [8.7–19.9%] (Figure 3). The proportion of low tidal variation areas differed over the six time points ($p = 0.0006$). All pairwise comparisons with respect to T3 showed significant differences. An example set of images is shown in Figure 4.

In an additional analysis, we demonstrate that one-third (nine subjects) of the subjects had a minimal (<5%) change, one-third (10 subjects) had more than a 5% increase, and one-third had more than a 5% decrease (11 subjects) of low tidal variation areas between T1 and T2. The group with the greatest reduction had significantly higher proportions of low tidal variation areas at baseline [median (IQR) 18.4% (15.0–27.3)] than the other two groups [median (IQR) 4.3% (0.5–11.4) and 7.7% (3.3–10.3); $p < 0.001$].

The mean [95% CI] GI indices at the different time points were T1 0.57 [0.54–0.60], T2 0.55 [0.51–0.58], T3 0.51 [0.49–0.54], T4 0.57 [0.53–0.61], T5 0.54 [0.50–0.60], and T6 0.60 [0.55–0.63] (Figure 5).

The proportion of GI indices differed over the six time points ($p < 0.0001$; Figure 3). All pairwise comparisons with respect to T3 showed significant differences. Additionally, we found significant differences between the following measurements: T2–T4 ($p = 0.036$) and T2–T6 ($p = 0.007$).

Six patients (20.0%) showed one [n = 4/6 (66.7%)] or two [n = 2/6 (33.3%)] episodes of desaturation $SpO_2 < 90\%$ intraoperatively during the surgical intervention. None of

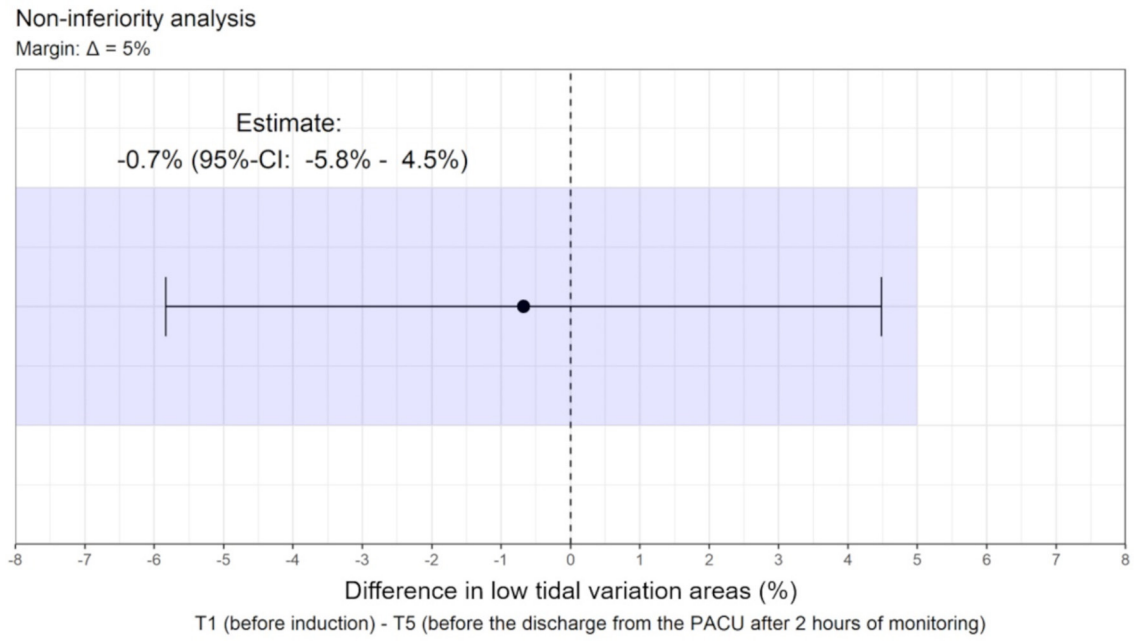


FIGURE 2
The mean difference in the percentage of low tidal variation areas between T1 and T5 and non-inferiority margin.

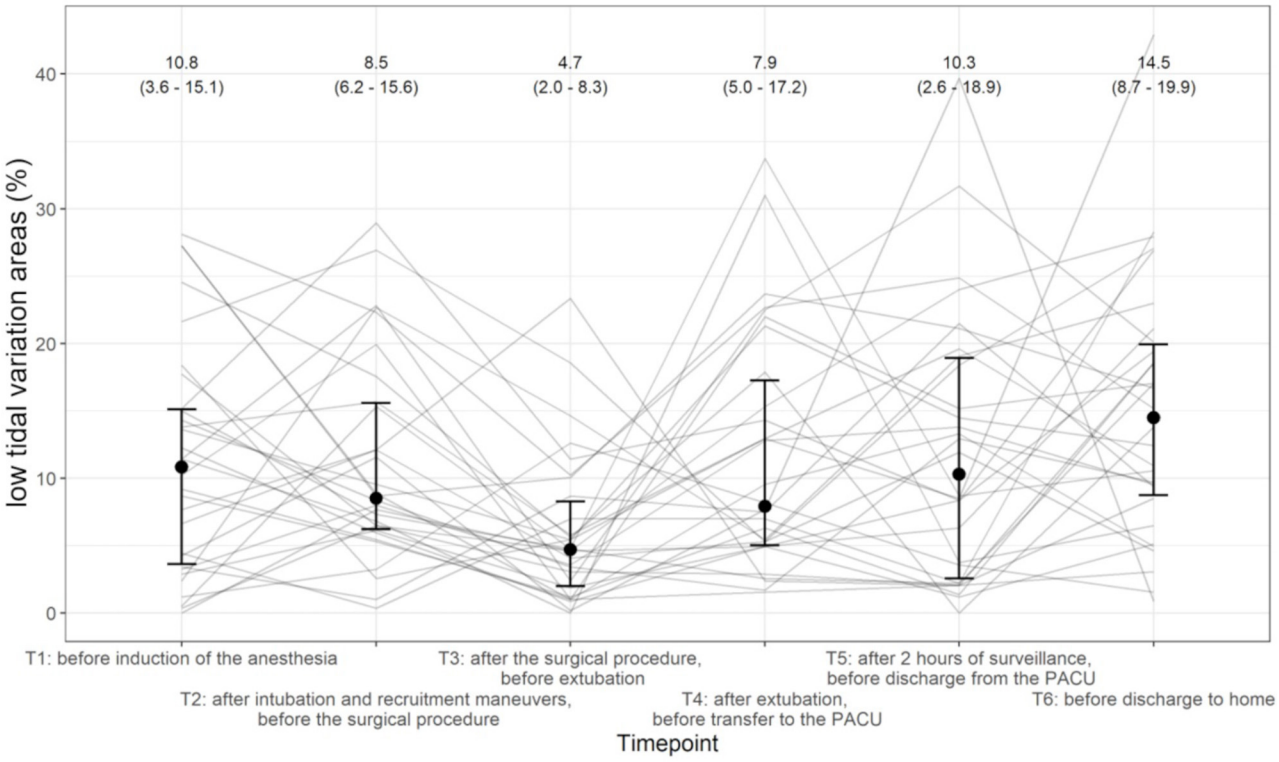


FIGURE 3
Evolution of proportion of low tidal variation areas across the different time points (T1 starting left until T6 on the right). Individual patients are shown as solid lines, and the median and interquartile range (IQR) at each time point are given.

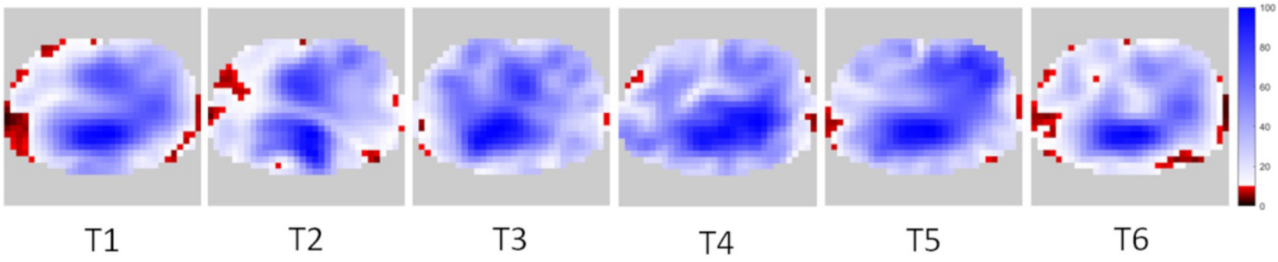


FIGURE 4
Example of distribution of low tidal variation areas (in red-black) at different time points.

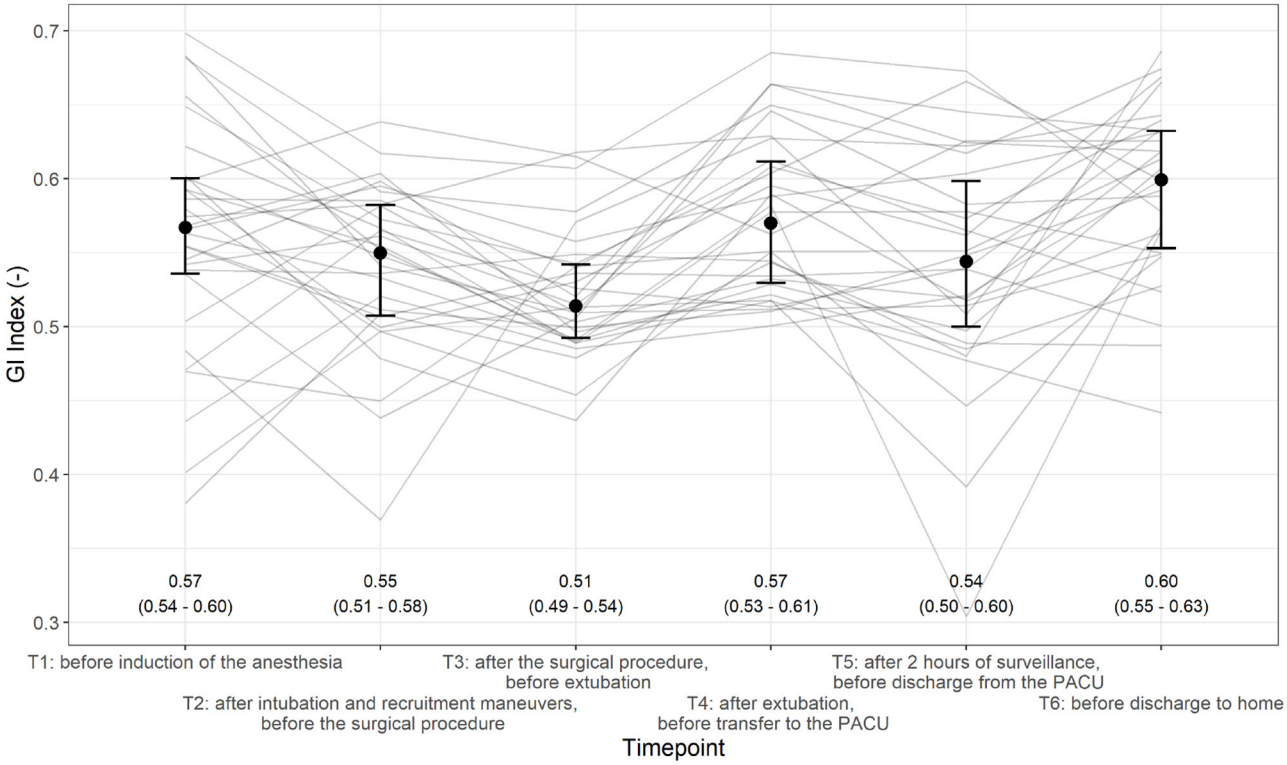


FIGURE 5
Evolution of the global inhomogeneity (GI) index across different time points (T1–T6). Individual patients are shown as solid lines, and the median and interquartile range (IQR) are given.

the patients reached any termination criteria during the procedure. Four patients showed one episode of desaturation SpO_2 < 90% during their PACU stay, which was treated with the administration of oxygen through a nasal cannula with a flow of 2–4 l/min.

None of the patients showed any postoperative pulmonary complications during the hospital stay. Seven patients (23.3%) required nasal oxygen with a flow of 1–3 l/min due to episodes of desaturation SpO_2 < 90% during the first 24 h. One patient showed thoracic pain limiting inspiration after discharge from PACU, and cardiac causes were excluded.

Follow-up

All patients were at home during the telephone follow-up on day 14 after the surgery. Only one patient (pre-known asthma) showed mild postoperative pulmonary complications (more dyspnea than before the surgical procedure). Self-treatment with

asthma medication occurred at home, with no medical presentation or re-hospitalization, not fulfilling the pre-defined criteria.

Discussion

This prospective observational trial showed that obese patients undergoing laparoscopic bariatric surgery do not leave the PACU with increased low tidal variation areas as detected preoperatively. This finding suggests that perioperative formation of atelectasis might be successfully inhibited with a regimen of 10 cm H_2O PEEP and repeated recruitment maneuvers.

The duration of laparoscopy and, thus, the increase in intra-abdominal pressure due to the pneumoperitoneum did not cause an increase in low tidal variation areas. On the contrary, after the termination of the pneumoperitoneum at T3 (after surgical procedure, before extubation), the GI index and the proportion of low tidal variation areas were significantly lower than at all other time points, suggesting the lowest rate of atelectasis and the most homogeneous ventilation during the entire perioperative period. This is particularly important, since in pneumoperitoneum, the dependent lung is expected to have increased rates of atelectasis (26). Our data indicate that an intraoperative ventilatory strategy with a volume-controlled mode with a tidal volume of 6–8 ml/kg, a PEEP of 10 cm H_2O, and repeated recruitment maneuvers may prevent atelectasis formation. A second explanation might be the almost upright positioning during bariatric surgery to optimize laparoscopic surgical conditions.

Our data show that atelectasis formation can be successfully prevented perioperatively in bariatric patients undergoing one of the commonplace minor surgeries with a pneumoperitoneum duration of <1 h. Our study included patients with a BMI < 40 with a median BMI of 45. These patients may benefit more from the ventilation strategy with a PEEP of 10 cm H_2O than patients with less pronounced obesity.

Since Futier et al. (10) showed the benefits of using lung protective ventilation in abdominal surgery, several studies have been performed to shed light on the best ventilation strategies. In the large PROVHILO trial, which included non-bariatric patients, the authors suggested using low PEEP and no recruitment maneuvers in open abdominal surgery (27). The PROBESE collaborative group postulated, in the largest trial with obese patients, that postoperative pulmonary complications could not be reduced by elevated PEEP levels or recruitment maneuvers (28). Other studies showed that PEEP levels of 10 cm H_2O with recruitment maneuvers improved respiratory parameters intraoperatively (29) and showed there was less postoperative atelectasis in the PACU (1, 29).

A published international consensus recommendation in 2019 (30) claimed that, although lung protective ventilation strategies could reduce postoperative pulmonary complications, there was still no consensus on its clinical use. Recommendations included individually titrated PEEP and performance of recruitment maneuvers with the lowest possible pressure over the shortest possible time, considered in an individual benefit–risk evaluation. Although this consensus does not solely pertain to bariatric patients, a BMI of >40 is regarded as one of the most significant risk factors for postoperative pulmonary complications, with an almost total agreement of experts (30). Nevertheless, it seems challenging to establish a direct relationship between intraoperative atelectasis and postoperative outcome (26).

Surprisingly, in the current study, this management not only prevented atelectasis formation but there was also no time point during the five EIT measures at which there was a significantly higher rate of low tidal variation areas than at baseline before administering hypnotics, oxygen, neuromuscular blocking agents, or opiates, thus matching the physiologic baseline of this patient group. This is surprising since reduced lung capacities and volumes during controlled ventilation and general anesthesia can lead to atelectasis in up to 90% of patients (31).

Different studies show that recruitment maneuvers and PEEP before extubation did not improve oxygenation in the PACU (32), an intraoperative regimen of increased PEEP level and recruitment maneuvers in bariatric patients did not reduce postoperative pulmonary complications (33), and PEEP and recruitment maneuvers for an open abdominal surgery cohort did not reduce postoperative pulmonary complications (27). In contrast, our data for this specific cohort of patients (BMI ≥ 40, laparoscopic surgery, pneumoperitoneum time <60 min, anti-Trendelenburg position) suggest an improvement regarding atelectasis formation due to the chosen anesthesia management (volume-controlled ventilation with 6–8 ml/kg, 10 cm H_2O PEEP, FiO_2 at 0.6, and recruitment maneuvers). However, what effect this ultimately has on postoperative pulmonary complications remains unclear.

These findings are consistent with data showing that recruitment maneuvers reduced pulmonary dysfunction in the PACU during laparoscopic bariatric surgeries (29) or that PEEP and recruitment maneuvers decreased atelectasis in bariatric patients (4). Recruitment maneuvers could lead to pulmonary conditions on a level comparable to preoperative conditions in obese patients (13). However, three standardized recruitment maneuvers were performed within a median of 64 min of the operation time, which does not often correspond to clinical reality, especially in prolonged procedures. In addition, patients are positioned in an anti-Trendelenburg position during laparoscopic bariatric procedures, which could reduce atelectasis compared with laparoscopic procedures in the supine position or the Trendelenburg position.

Limitations of this study include the single-center design and the lack of randomization with the absence of a control group (without PEEP of 10 cm H_2O and recruitment maneuvers). Nevertheless, we demonstrated an absence of significant low tidal variation areas in this cohort. There are some more limitations in the measurement technique itself. First, the EIT belt was placed in the same position on the skin of the patients, but postural changes among measurements, muscle paralysis, and capnoperitoneum could all affect the position and geometry of the lungs inside the chest. However, the measurements for the primary outcome should not be affected because all measurements were performed under identical conditions. We cannot exclude an effect of the described phenomenon on our secondary outcomes. Second, we used a modified analysis algorithm for low tidal variation areas compared to the original publication describing the so-called silent spaces. The original technique, analyzing only pixels within

anatomically (CT-derived) defined lung regions, carries the risk of underestimating minimally ventilated lung areas (21). This is the case when the assumed lung areas do not match the effective anatomy of the measured lung. Our analysis technique avoids a priori assumptions and takes into account all pixels of the reconstructed EIT image. This approach tends to overestimate the low tidal variation areas because areas outside the lung are also included. For the comparison of different time points in the same patient, we believe that the second analysis technique is better suited because, with this technique, all minimally ventilated lung segments are included in the analysis. The sensitivity and specificity of silent spaces measured by EIT are not known and its accuracy depends on the "right" assumptions regarding lung anatomy (33). Nevertheless, the relevance of this finding on repetitive measurements of low tidal variation areas in the same subject remains unclear. Additionally, there is evidence that the change in silent spaces correlates well with lung recruitment measured using the P-V curve technique (19).

Conclusion

Obese patients undergoing laparoscopic bariatric surgery do not leave the PACU with an increased rate of low tidal variation areas as detected preoperatively. Thus, we suggest applying 10 cm H_2O PEEP and repeated recruitment maneuvers perioperatively to potentially prevent atelectasis formation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethikkommission für die Forschung am Menschen, Bern. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MB, LR, MK, ML, TRiv, and AV contributed to the study design, study conduct, analysis, manuscript preparation, patient recruitment, and manuscript finalization. AF contributed to the study design, study conduct, analysis, and manuscript preparation. MH helped with the statistical analysis. TRie contributed to the study design, study conduct, analysis, manuscript preparation, statistical analysis, and finalizing the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by research grant from the Department of Anaesthesiology and Pain Medicine, Inselspital Bern.

Acknowledgments

We thank all participating patients. We thank the staff of the Department of Anaesthesiology and Pain Medicine, Inselspital, especially the section on anesthesia for visceral surgery and the post-anesthesia care unit. We thank all nurses in the ward of visceral surgery for their support in performing the study.

Conflict of interest

TRiv receives support from Fisher & Paykel Healthcare (New Zealand) for other projects in the form of supplies for free or at a reduced price. TRie receives consultancy fees from Sentec AG, Switzerland. AV receives consultancy fees as a member of the Advisory Board of MSD, Merck Switzerland.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Talab HF, Zabani IA, Abdelrahman HS, Bukhari WL, Mamoun I, Ashour MA, et al. Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. *Anesth Analg.* (2009) 109:1511–6. doi: 10.1213/ANE.0b013e3181ba7945

2. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. *Int J Gen Med.* (2010) 3:335–43. doi: 10.2147/IJGM.S11926

3. Fernandez-Bustamante A, Frendl G, Sprung J, Kor DJ, Subramaniam B, Martinez Ruiz R, et al. Postoperative pulmonary complications, early mortality, and hospital stay following noncardiothoracic surgery: a multicenter study by the perioperative research network investigators. *J Am Med Assoc Surg.* (2017) 152:157–66. doi: 10.1001/jamasurg.2016.4065

4. Reinius H, Jonsson L, Gustafsson S, Sundbom M, Duvernoy O, Pelosi P, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia

and paralysis: a computerized tomography study. *Anesthesiology*. (2009) 111:979–87. doi: 10.1097/ALN.0b013e3181b87edb

5. De Jong A, Chanques G, Jaber S. Mechanical ventilation in obese ICU patients: from intubation to extubation. *Crit Care*. (2017) 21:63. doi: 10.1186/s13054-017-1641-1

6. Eichenberger A, Proietti S, Wicky S, Frascarolo P, Suter M, Spahn DR, et al. Morbid obesity and postoperative pulmonary atelectasis: an underestimated problem. *Anesth Analg*. (2002) 95:1788–92. doi: 10.1097/00000539-200212000-00060

7. Futier E, Paugam-Burtz C, Godet T, Khoy-Ear L, Rozencwajg S, Delay JM, et al. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). *Intensive Care Med*. (2016) 42:1888–98. doi: 10.1007/s00134-016-4594-y

8. Rothen HU, Sporre B, Engberg G, Wegenius G, Hedenstierna G. Reexpansion of atelectasis during general anaesthesia may have a prolonged effect. *Acta Anaesthesiol Scand*. (1995) 39:118–25. doi: 10.1111/j.1399-6576.1995.tb05602.x

9. Rothen HU, Neumann P, Berglund JE, Valtysson J, Magnusson A, Hedenstierna G. Dynamics of re-expansion of atelectasis during general anaesthesia. *Br J Anaesth*. (1999) 82:551–6. doi: 10.1093/bja/82.4.551

10. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. (2013) 369:428–37. doi: 10.1056/NEJMoa1301082

11. Ball L, Hemmes SNT, Serpa Neto A, Bluth T, Canet J, Hiesmayr M, et al. Intraoperative ventilation settings and their associations with postoperative pulmonary complications in obese patients. *Br J Anaesth*. (2018) 121:899–908. doi: 10.1016/j.bja.2018.04.021

12. Stankiewicz-Rudnicki M, Gaszynski W, Gaszynski T. Assessment of ventilation distribution during laparoscopic bariatric surgery: an electrical impedance tomography study. *Biomed Res Int*. (2016) 2016:7423162. doi: 10.1155/2016/7423162

13. Nestler C, Simon P, Petroff D, Hammermüller S, Kamrath D, Wolf S, et al. Individualized positive end-expiratory pressure in obese patients during general anaesthesia: a randomized controlled clinical trial using electrical impedance tomography. *Br J Anaesth*. (2017) 119:1194–205. doi: 10.1093/bja/aex192

14. Riva T, Pascolo F, Huber M, Theiler L, Greif R, Disma N, et al. Evaluation of atelectasis using electrical impedance tomography during procedural deep sedation for MRI in small children: a prospective observational trial. *J Clin Anesth*. (2022) 77:110626. doi: 10.1016/j.jclinane.2021.110626

15. Zhao Z, Möller K, Steinman D, Frerichs I, Guttmann J. Evaluation of an electrical impedance tomography-based Global Inhomogeneity Index for pulmonary ventilation distribution. *Intensive Care Med*. (2009) 35:1900–6. doi: 10.1007/s00134-009-1589-y

16. Adler A, Arnold JH, Bayford R, Borsic A, Brown B, Dixon P, et al. GREIT: a unified approach to 2D linear EIT reconstruction of lung images. *Physiol Meas*. (2009) 30:S35–55. doi: 10.1088/0967-3334/30/6/S03

17. Yorkey TJ, Webster JG, Tompkins WJ. Comparing reconstruction algorithms for electrical impedance tomography. *IEEE Trans Biomed Eng*. (1987) 34:843–52. doi: 10.1109/TBME.1987.326032

18. Schnidrig S, Casaulta C, Schibler A, Riedel T. Influence of end-expiratory level and tidal volume on gravitational ventilation distribution during tidal breathing in healthy adults. *Eur J Appl Physiol*. (2013) 113:591–8. doi: 10.1007/s00421-012-2469-7

19. Wettstein M, Radlinger L, Riedel T. Effect of different breathing aids on ventilation distribution in adults with cystic fibrosis. *PLoS ONE*. (2014) 9:e106591. doi: 10.1371/journal.pone.0106591

20. Spadaro S, Mauri T, Bohm SH, Scaramuzzo G, Turrini C, Waldmann AD, et al. Variation of poorly ventilated lung units (silent spaces) measured by electrical impedance tomography to dynamically assess recruitment. *Crit Care*. (2018) 22:26. doi: 10.1186/s13054-017-1931-7

21. Ukere A, März A, Wodack KH, Trepte CJ, Haese A, Waldmann AD, et al. Perioperative assessment of regional ventilation during changing body positions and ventilation conditions by electrical impedance tomography. *Br J Anaesth*. (2016) 117:228–35. doi: 10.1093/bja/aew188

22. von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO. The impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. *Anesth Analg*. (2007) 104:1364–8. doi: 10.1213/01.ane.0000261503.29619.9c

23. Park J, Lee EK, Lee JH, Oh EJ, Min JJ. Effects of inspired oxygen concentration during emergence from general anaesthesia on postoperative lung impedance changes evaluated by electrical impedance tomography: a randomised controlled trial. *J Clin Monit Comput*. (2019) 19:390. doi: 10.1007/s10877-019-00390-0

24. Conover WJ. *Practical Nonparametric Statistics*. 3rd ed. Wiley Series in Probability and Statistics, Hoboken, NJ: John Wiley & Sons Inc (1999).

25. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2018).

26. Lagier D, Zeng C, Fernandez-Bustamante A, Vidal Melo MF. Perioperative pulmonary atelectasis: part II. *Clin Implicat Anesthesiol*. (2022) 136:206–36. doi: 10.1097/ALN.0000000000004009

27. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet*. (2014) 384:495–503. doi: 10.1016/S0140-6736(14)60416-5

28. Bluth T, Teichmann R, Kiss T, Bobek I, Canet J, Cinnella G, et al. Protective intraoperative ventilation with higher versus lower levels of positive end-expiratory pressure in obese patients (PROBESE): study protocol for a randomized controlled trial. *Trials*. (2017) 18:202. doi: 10.1186/s13063-017-1929-0

29. Yildiz AM, Kilinç G, Sungurtekin H, Karaduman S, Birsen O. Impact of positive end-expiratory pressure with alveolar recruitment maneuver on respiratory and oxygenation parameters of patients during laparoscopic bariatric surgery. *Eur Rev Med Pharmacol Sci*. (2022) 26:9170–9. doi: 10.26355/eurrev_202212_30668

30. Young CC, Harris EM, Vacchiano C, Bodnar S, Bukowy B, Elliott RRD, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. *Br J Anaesth*. (2019) 123:898–913. doi: 10.1016/j.bja.2019.08.017

31. Degani-Costa LH, Faresin SM, dos Reis Falcão LF. Preoperative evaluation of the patient with pulmonary disease. *Braz J Anesthesiol*. (2014) 64:22–34. doi: 10.1016/j.bjane.2012.11.002

32. Bluth T, Serpa Neto A, Schultz MJ, Pelosi P, Gama de Abreu M, Gregoretti C, et al. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs. low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. *J Am Med Assoc*. (2019) 321:2292–305. doi: 10.1001/jama.2019.7505

33. Severac M, Chiali W, Severac F, Perus O, Orban JC, Iannelli A, et al. Alveolar recruitment manoeuvre results in improved pulmonary function in obese patients undergoing bariatric surgery: a randomised trial. *Anaesth Crit Care Pain Med*. (2021) 40:100775. doi: 10.1016/j.accpm.2020.09.011

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 August 2023
DOI 10.3389/fmed.2023.1224242

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Boon Hau Ng,
Universiti Kebangsaan Malaysia Medical Center (UKMMC), Malaysia
Oleksandr Nazarchuk,
National Pirogov Memorial Medical University, Ukraine
Dmytro Dmytriiev,
National Pirogov Memorial Medical University, Ukraine

*CORRESPONDENCE
Francesca Simioli
✉ francesimioli@gmail.com

RECEIVED 17 May 2023
ACCEPTED 17 August 2023
PUBLISHED 31 August 2023

CITATION
Simioli F, Annunziata A, Coppola A, Imitazione P, Mirizzi AI, Marotta A, D'Angelo R and Fiorentino G (2023) The role of dexmedetomidine in ARDS: an approach to non-intensive care sedation.
Front. Med. 10:1224242.
doi: 10.3389/fmed.2023.1224242

The role of dexmedetomidine in ARDS: an approach to non-intensive care sedation

Francesca Simioli*, Anna Annunziata, Antonietta Coppola, Pasquale Imitazione, Angela Irene Mirizzi, Antonella Marotta, Rossella D'Angelo and Giuseppe Fiorentino

Department of Respiratory Pathophysiology and Rehabilitation, Monaldi Hospital, A.O. dei Colli, Naples, Italy

Introduction: Severe COVID-19 is a life-threatening condition characterized by complications such as interstitial pneumonia, hypoxic respiratory failure, and acute respiratory distress syndrome (ARDS). Non-pharmacological intervention with mechanical ventilation plays a key role in treating COVID-19-related ARDS but is influenced by a high risk of failure in more severe patients. Dexmedetomidine is a new generation highly selective α2-adrenergic receptor (α2-AR) agonist that provides sedative effects with preservation of respiratory function. The aim of this study is to assess how dexmedetomidine influences gas exchange during non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) in moderate to severe ARDS caused by COVID-19 in a non-intensive care setting.

Methods: This is a single center retrospective cohort study. We included patients who showed moderate to severe respiratory distress. All included subjects had indication to NIV and were suitable for a non-intensive setting of care. A total of 170 patients were included, divided in a control group ($n = 71$) and a treatment group (DEX group, $n = 99$).

Results: A total of 170 patients were hospitalized for moderate to severe ARDS and COVID-19. The median age was 71 years, 29% females. The median Charlson comorbidity index (CCI) was 2.5. Obesity affected 21% of the study population. The median pO_2/FiO_2 was 82 mmHg before treatment. After treatment, the increase of pO_2/FiO_2 ratio was clinically and statistically significant in the DEX group compared to the controls (125 mmHg [97–152] versus 94 mmHg [75–122]; $^{***}p < 0.0001$). A significative reduction of NIV duration was observed in DEX group (10 [7–16] days vs. 13 [10–17] days; $^{*}p < 0.02$). Twenty four patients required IMV in control group ($n = 71$) and 16 patients in DEX group ($n = 99$) with a reduction of endotracheal intubation of 62% (OR 0.38; $^{**}p < 0.008$). A higher incidence of sinus bradycardia was observed in the DEX group.

Conclusion: Dexmedetomidine provides a "calm and arousal" status which allows spontaneous ventilation in awake patients treated with NIV and HFNC. The adjunctive therapy with dexmedetomidine is associated with a higher pO_2/FiO_2, lower duration of NIV, and a lower risk of NIV failure. A higher incidence of sinus bradycardia needs to be considered.

KEYWORDS

acute respiratory distress syndrome, non-invasive ventilation, continuous positive airway pressure, pressure support ventilation, high flow nasal cannula, refractory hypoxemia, COVID-19, respiratory drive

Introduction

COVID-19 is a systemic infection caused by a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the beta family of coronaviruses (1). This virus rapidly spread from Wuhan in China, where it was first isolated, around many countries, causing a pandemic in a few weeks. In January 2020, the director of the world health organization (WHO) declared this event a public health emergency of international concern. By then, all continents had been involved in the pandemic. Italy was early affected by this emergency. Since the first COVID-19 patient in Italy in early 2020, more than 18 million cases and approximately 167,842 deaths have been recorded (2).

The clinical manifestations of SARS-CoV-2 infection widely range between completely asymptomatic cases and critical illness. Severe COVID-19 is a life-threatening condition characterized by complications such as interstitial pneumonia, hypoxic respiratory failure, acute respiratory distress syndrome (ARDS), and pneumomediastinum. Information about the incidence and management of critically ill patients diagnosed with COVID-19 and ARDS are still controversial. Risk factors that have been correlated with a poor prognosis included old age, comorbidities such as systemic hypertension, diabetes mellitus, morbid obesity, chronic pulmonary disease, coronary artery disease, chronic kidney disease, and malignancies (3, 4).

The scientific community faced a significant challenge caused by the pandemic, resulting in several research protocols conducted with therapeutical agents since 2020. A possible indication was tested for a number of active principles, including drugs that modulate the inflammatory response during the infection, such as anti-IL-6R monoclonal antibodies, chloroquine, and hydroxychloroquine, as well as antiviral therapies with various mechanisms of action, for example, neuraminidase inhibitors, inhibitors of DNA and RNA synthesis, lastly a nucleoside analogs inhibitor of the RNA dependent RNA polymerase (RdRp) of coronaviruses. Although some of the drugs showed encouraging results in clinical trials, there is still a major perplexity concerning the severe forms of the disease. Undoubtedly, most of the COVID-19 related deaths are caused by a critical impairment of the lungs and ARDS with alveolar and interstitial damage. The organ damage follows the viral infection and hyper-inflammation phase; finally, it can progress to the point of no return in which reducing the viral load or modulating the inflammation become less relevant targets.

Non-pharmacological intervention with mechanical ventilation plays a key role in treating COVID-19 related ARDS. Non-invasive ventilation (NIV) has been widely accepted in the management of acute respiratory failure, with strong evidence for its benefit in patients with cardiogenic pulmonary edema (5) and acute exacerbations of chronic obstructive pulmonary disease (COPD) (6). Over time NIV has become an established approach for ARDS since it can avoid intubation when used as a first-line intervention in a specific setting with good expertise in ventilation (7). More recently, a review on COVID-19, including 23 manuscripts and 4,776 patients, revealed an appalling NIV failure rate of 47% and an intubation rate of 26.5% (8). At the same time, some authors suggest that high flow nasal cannula (HFNC) can also be successful in selected patients with severe respiratory failure caused by SARS-CoV-2 infection (9). Still the evidence is very poor and debatable.

Dexmedetomidine is a new generation highly selective α2-adrenergic receptor (α2-AR) agonist that provides sedative and analgesic effects, cardiovascular stabilizing effects, and preservation of respiratory function (10). In mechanically ventilated adults, the use of dexmedetomidine, compared to other sedatives, resulted in a lower risk of delirium and a modest reduction in duration of mechanical ventilation and ICU stay but increased the risks of bradycardia and hypotension (11). Scarce evidence is available about the effects of gas exchange during NIV in COVID-19 related ARDS. All the studies about dexmedetomidine are conducted in ICU. There is insufficient evidence about NIV and HFNC in a non-intensive setting of care.

Aim

The aim of this study is to assess how dexmedetomidine influences gas exchange during NIV and HFNC in moderate to severe ARDS caused by COVID-19 in a non-intensive setting of care. The primary outcomes were the pO_2/FiO_2 ratio and the respiratory rate. This study also aims to evaluate the effect of dexmedetomidine on the risk of NIV failure. Secondary outcomes were the intubation rate and the mortality rate.

Methods

This is a single center retrospective cohort study. Data were collected from patients who were hospitalized in the sub-intensive therapy respiratory unit at Cotugno Hospital in Naples, Italy, during the COVID-19 pandemic, during 2022, in the post vaccinal era. A total of 215 patients showed acute respiratory failure and moderate to severe respiratory distress at admission. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (pO_2/FiO_2 ratio) was 200 or lower. All subjects were tested positive for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay on a nasopharyngeal swab. All subjects showed interstitial pneumonia with critical extension compatible with severe COVID-19, assessed by a chest's high-resolution computed tomography (HRCT). A multidisciplinary evaluation at baseline was performed to evaluate the indication to invasive versus non-invasive ventilation; inclusion criteria for NIV were: acute respiratory failure, $pH \geq 7.15$, $pCO_2 < 100$ mmHg, $pO_2 \leq 60$ mmHg in room air, respiratory rate ≥ 20 per minute, preserved consciousness with Glasgow coma scale (GCS) at least 9, cardiogenic pulmonary oedema, acute hypoxemic respiratory failure in immunocompromised patients. Exclusion criteria for NIV were: cardiac arrest, respiratory arrest, encephalopathy with GCS ≤ 8, facial trauma, inability to fit the mask, major bleeding, uncontrolled upper gastrointestinal bleeding, fixed upper airway obstruction, inability to protect the upper airway, high risk of aspiration. A total of 170 patients had indication to NIV and were suitable for a non-intensive setting of care. A total of 170 patients were included as reported in Figure 1.

At admission, we recorded baseline features: gender, age, BMI and vaccinal status. Concomitant diseases were recorded and the Charlson comorbidity index (CCI) was calculated. CCI is a method of categorizing patients' comorbidities that predicts the long-term mortality risk (12). The baseline pO_2/FiO_2 ratio was determined by blood gas analysis. Ventilation support needed at the time of

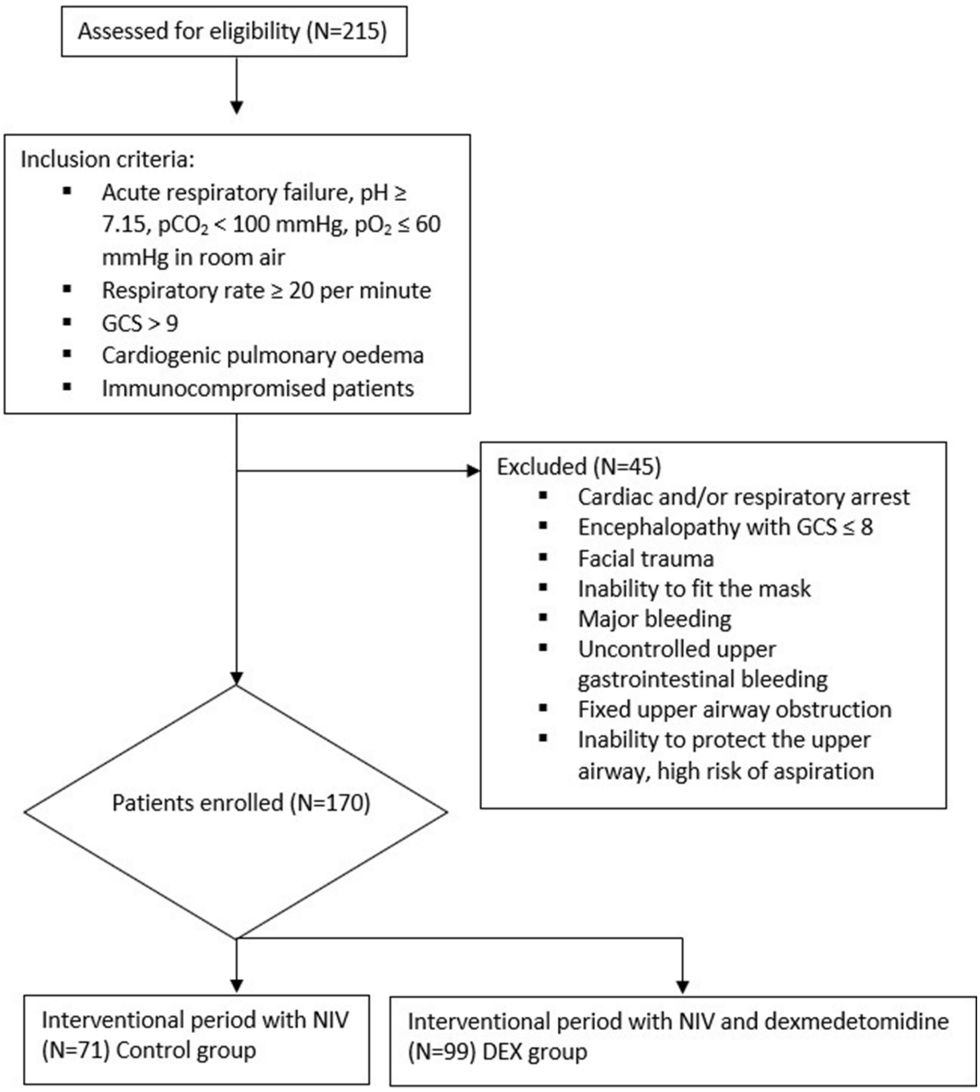


FIGURE 1
Protocol intervention, inclusion/exclusion criteria.

admission, respiratory rate (RR), and FiO_2 were recorded. Blood gas analysis was repeated at 2 h after treatment initiation. Subsequently, blood gas analysis was repeated every 6 h. C-reactive protein (CRP) and other markers were tested on blood samples at admission and repeated after treatment initiation in a range of 12–24 h.

The type of respiratory support was chosen based on blood gas analysis, acid–base disorders such as acidosis, the patient's ventilatory demand and subjective preference, but also the local availability resulted to be determinant during the pandemic. Seventy one subjects received respiratory support and the pharmacological standard of care (control group). Ninety nine subjects received adjunctively dexmedetomidine (DEX group). The administration of sedation depended on the patient's general status of anxiety and acceptance of ventilation. The two groups were similar considering age, gender, comorbidities, ARDS severity, pO_2/FiO_2, respiratory rate, lactates and CRP.

The dexmedetomidine was initiated precociously after NIV administration. The induction of sedation was performed with promazine. The initial dose of dexmedetomidine was 0.3 mcg/kg/h. The maintenance dose of dexmedetomidine ranged between 0.2 and 0.8 mcg/kg/h with a continuous intravenous (IV) infusion. The dose was targeted on the patient's response, RR, level of consciousness, NIV tolerance and adaptation. Among these, we aimed to have a RR below 25, and a "calm and arousal" status in which the patients were alert and responsive to verbal stimulation. The average dose used during the study was 0.4 mcg/kg/h. During the hospitalization, we recorded what changes in respiratory support and FiO_2 were needed, as well as the adopted interfaces. We also recorded the duration of NIV in terms of days of treatment before weaning to conventional oxygen therapy (COT). Need for intubation, invasive mechanical ventilation (IVM) and relocation to (ICU) were observed as surrogate outcomes for NIV failure. Mortality was estimated at 30 days from NIV administration. The tolerance to NIV was observed, which included delirium, fighting the ventilator, and pulling the mask. Finally, eventual adverse reactions, especially those on the cardiovascular system, were evaluated.

This study was approved by the local ethics committee of University of Campania "Luigi Vanvitelli" and A.O. dei Colli in accordance with the 1976 Declaration of Helsinki and its later amendments, protocol number: AOC-0020053-2020. All patients were treated accordingly to the local standard of care.

Results are reported as number and percentage for categorical variables and mean and standard deviation (SD) for continuous variables. The mean values of the control group and DEX group were compared using a *t*-test. Confidence interval (CI) was set at 95%, and the significance level was <0.05. The rate of IMV and 30-day mortality rate between the groups were compared using odds ratio (OR).

Results

A total of 170 patients were hospitalized for moderate to severe ARDS and COVID-19. The median age was 71 years, 29% were females. The median CCI was 2.5. Obesity affected 21% of the study population. All subjects were affected by acute respiratory failure with a median pO_2/FiO_2 ratio of 82 mmHg before treatment. The baseline features are described in Table 1. Seventy one patients underwent NIV or HFNC and the standard of care of treatment (control group), 99 patients adjunctively received dexmedetomidine (DEX group). No significant difference was observed at baseline between the two groups, as showed in Table 1.

The HFNC was administered with a mean flow of 60 L/min. The mean positive end expiratory pressure (PEEP) in the CPAP mode was 8 cm H_2O. The mean pressure support (PS) and expiratory positive airway pressure (EPAP) in the NIV—PSV mode was 12 and 8 cm H_2O, respectively.

After treatment, the pO_2/FiO_2 ratio clearly increased in both groups compared to baseline (106 vs. 82 mmHg in the total cohort); the increase was clinically and statistically significant in the DEX group compared to the controls (125 mmHg [97–152] vs. 94 mmHg [75–122]; 95% CI 16.46–45.54; ***$p < 0.0001$). The RR improved at the same time, without a significant difference between the DEX and the control group (24 [20–26] pm vs. 26 [22–26] pm; p = ns). No significant difference was observed on other biochemical tests, including CRP (5 vs. 5 mg/dL; p = ns). The results are reported in Table 2.

A significative reduction of NIV duration was observed in DEX group (10 [7–16] days vs. 13 [10–17] days; 95% CI −5.53 to −0.47; *$p < 0.02$). Twenty four patients required IMV in control group ($n = 71$) and 16 patients in DEX group ($n = 99$) with a reduction of endotracheal intubation of 62% (OR 0.38; 95% CI 0.18–0.78; **$p < 0.008$). The 30-days mortality was calculated among non-invasively ventilated patients, 16 deaths were recorded in control group and 12 in DEX group with a non-significant reduction of the risk of death (OR 0.47; 95% CI 0.21–1.07; $p < 0.07$).

Outcomes on gas exchange and NIV failure are reported in Figures 2, 3.

Hypotension was observed in 11% of the total population during hospitalization, the incidence was similar between DEX and the control group (12% vs. 10%). Bradycardia occurred in 25% of cases and was frequently associated with dexmedetomidine administration (30%). A minority of those effects were considered severe and led to dexmedetomidine discontinuation. Tachyarrhythmia was observed in 4.7% of the population with a comparable incidence between the groups.

Intolerance to NIV was very frequent in our study population (33.5%). Delirium was observed more frequently in the control group than DEX (22% vs. 16%), but no significant difference was observed (OR 0.67; 95% CI 0.35–1.26; $p = 0.22$) (Table 3).

TABLE 1 Characteristics before treatment.

	Total cohort $n = 170$	Control $n = 71$	DEX $n = 99$	p
Age, years	71 (61–80)	70 (60.5–80)	71 (61–79)	0.56
Female	49 (29%)	19 (27%)	30 (30%)	
Charlson comorbidity index	2.5 (2–4)	2.5 (1.5–4)	2.75 (2–5)	0.24
Obesity (BMI > 30)	36 (21.17%)	17 (23.9%)	19 (19%)	0.20
pO_2/FiO_2, mmHg	82 (69–108)	82 (72–120)	82 (68–105)	0.14
Respiratory rate (RR), pm	30 (28–34)	30 (28–33)	30 (28–34)	0.33
FiO_2, %	80 (60–95)	80 (60–95)	80 (66–95)	0.45
Lactate, mmol/L	1 (1–5)	2 (1–5)	1 (1–5)	0.23
C-reactive protein (CRP), mg/dL	6 (3–10)	6 (3–9.5)	6 (3–10)	0.32
SARS-CoV-2 vaccine	110 (64.7%)	46 (64.8%)	64 (64.6%)	

Results are expressed as median and IQR or number and percentage.

TABLE 2 Characteristics after treatment.

	Total cohort ($n = 170$)	Control ($n = 71$)	DEX ($n = 99$)	p
Respiratory support				
- HFNC	83 (49%)	38 (53%)	45 (46%)	
- CPAP	41 (24%)	16 (23%)	25 (25%)	
- NIV	46 (27%)	17 (24%)	29 (29%)	
pO_2/FiO_2, mmHg	106 (90–148)	94 (75–122)	125 (97–152)	0.0001***
RR, pm	24 (20–26)	26 (22–28)	24 (20–26)	0.07
Lactate, mmol/L	2 (1–5)	2 (1–5)	2 (1–6)	0.83
CRP, mg/dL	5 (2–8)	5 (2–8)	5 (3–8)	0.73
NIV duration, days	11 (8–16)	13 (10–17)	10 (7–16)	0.02*
IMV, %	40 (23.5%)	24 (33.8%)	16 (16%)	0.008**
30 days mortality, %	30 (17.6%)	16 (25.4%)	12 (12.1%)	0.07

Median and IQR or number and percentage. *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

Discussion

The main purpose of the study was to investigate the effects of dexmedetomidine on gas exchange during NIV and HFNC in

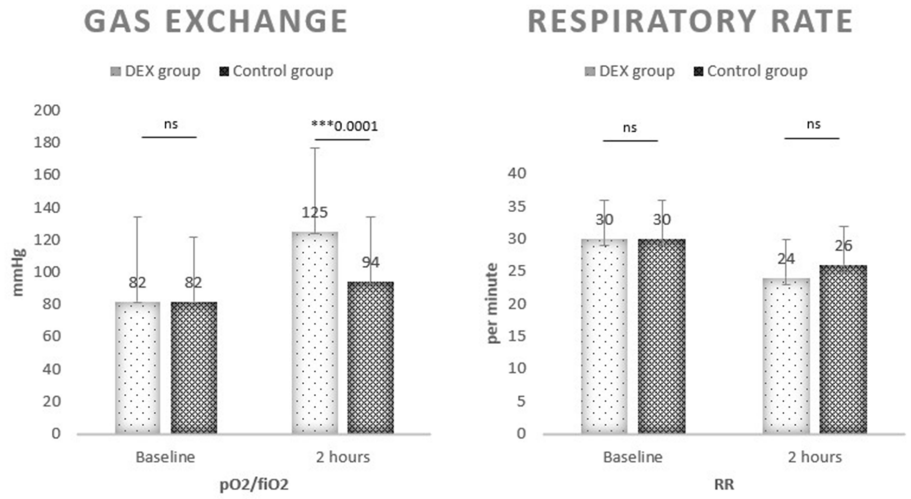


FIGURE 2
pO_2/FiO_2 improved in DEX group; respiratory rate was comparable.

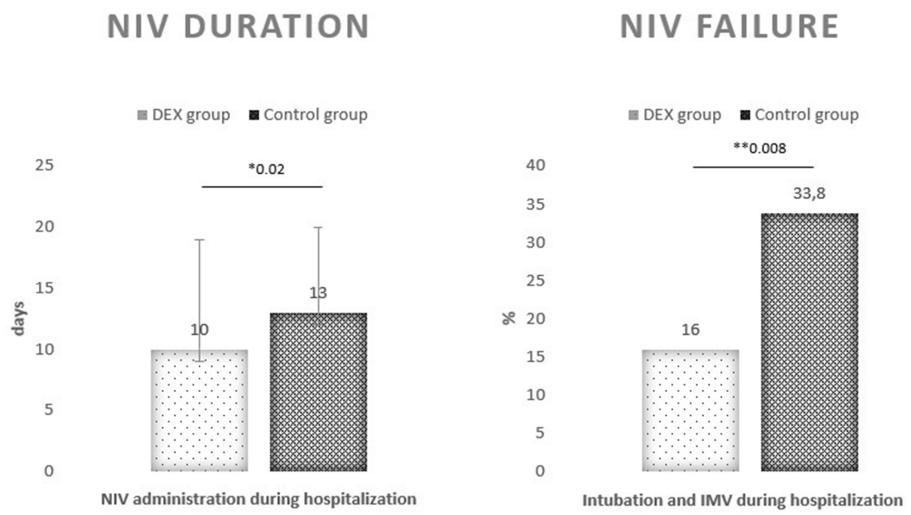


FIGURE 3
Non-invasive ventilation was needed for a shorter time in DEX group compared to controls. Invasive mechanical ventilation (IMV) rate was lower in DEX group.

TABLE 3 Concomitant observations and adverse drug reactions.

	Total cohort	Control	DEX
Hypotension	19 (11.2%)	7 (10%)	12 (12%)
Bradycardia	45 (25.3%)	13 (18.3%)	30 (30%)
Tachyarrhythmia	8 (4.7%)	3 (4.2%)	5 (5%)
NIV intolerance	64 (33.5%)	26 (36.6%)	31 (31%)
Delirium	31 (18.23%)	16 (22.53%)	15 (16%)

moderate to severe ARDS caused by COVID-19 in a non-intensive setting of care. Dexmedetomidine is an α2-adrenoceptor agonist with sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, and minimal depression of respiratory function. It is potent and highly selective for α2-receptors with an α2:α1 ratio of 1,620:1. Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic α2-receptors in the locus coeruleus, thereby inducting a state of unconsciousness similar to natural sleep, with the unique aspect that patients remain easily rousable and cooperative. Dexmedetomidine is rapidly distributed and is mainly hepatically metabolized into inactive metabolites by glucuronidation and hydroxylation. A high inter-individual variability in dexmedetomidine pharmacokinetics has been described, especially in the intensive care unit population. In recent years, multiple pharmacokinetic non-compartmental analyses as well as population pharmacokinetic studies have been performed. Body size, hepatic impairment, and presumably plasma albumin and cardiac output have a significant impact on dexmedetomidine pharmacokinetics. As central α1-adrenoceptor activation counteracts the sedative α2 effects,

dexmedetomidine is a more potent sedative than clonidine. An important feature of dexmedetomidine-based sedation is that patients remain easily rousable. This aspect, combined with the minimal influence on respiration, makes dexmedetomidine an interesting alternative sedative in many procedures, such as awake craniotomies and conscious sedation of non-intubated patients prior to and/or during surgical and other procedures (13). Despite this, dexmedetomidine use is actually confined to intensive care. The aim of the study was to test its use in a non-intensive setting of care.

As the primary outcome, we measured the pO_2/FiO_2 ratio, which significantly improved in the DEX group. This observation suggests a positive effect on oxygenation without the risk of significant respiratory depression for all types of respiratory support; in fact, 52% of the patients enrolled received HFNC, 46% in the DEX group. The respiratory rate instead was similar in the two groups, thus suggesting that the pattern of breathing was guaranteed by the respiratory support and the patient's effort itself even during sedation. COVID-19 related ARDS is characterized by high work of breathing and ventilatory demand, and this has been associated with self-inflicted lung injury (14). Patients in the DEX group were "calm and arousal" and maintained spontaneous ventilation. We can speculate that dexmedetomidine contributed to matching the patient's ventilatory demand, avoiding unregulated and prolonged efforts. We included patients with moderate to severe ARDS with pO_2/FiO_2 ratio < 200, but they were mostly severe considering the mean pO_2/FiO_2 ratio of 82 at baseline. We decided to include all types of respiratory therapy, also considering that during pandemic the initial therapy was partially influenced by local availability beyond clinical considerations or laboratory features. Among the overall population, 49% received HFNC, 24% CPAP, and 27% NIV (pressure support). The average needed FiO_2 was 0.80 in both groups. The wide heterogeneity of respiratory therapies may represent a limit, and it was considered as a confounding factor during the data analysis process. Nevertheless, we chose to include all possible respiratory therapies in relation to real life practice, and also because we aimed to test the adaption to ventilation besides the physiological effects of different therapies. Many patients worsen not because receiving inappropriate therapy, but they may not benefit of them because of agitation and asynchronies, leading to an increased work of breathing, fatigue and lower oxygenations despite alveolar recruitment. This study also aims to evaluate the effect of dexmedetomidine on the risk of NIV failure. The treatment group showed a smaller duration of ventilation (10 days) and a smaller intubation rate (16%). According to the literature, dexmedetomidine is a strategy to improve NIV comfort; it reduces the need for intubation and mechanical ventilation in adults with acute respiratory failure in ICU (15). Our observation brings dexmedetomidine outside ICU, and it has to be considered a safe adjunctive therapy for COVID-19 with associated acute respiratory failure for its effects on gas exchange and comfort. NIV intolerance was unsurprisingly common in our population and was similarly observed in both groups at baseline (33.5%). As a matter of fact, the adhesion to therapy and cooperation, which is fundamental in awake patients, clinically improved with continuous dexmedetomidine infusion. Delirium was as common as data reported by ICU-based studies. Nevertheless, we observed a significant reduction of delirium in DEX group compared to no sedation (16% vs. 22%). This finding likely explains the lower need for IMV and the lower mortality overall.

A large observational study reported that NIV is used to treat ARDS in ICU, but IMV should be adopted for severe ARDS with pO_2/FiO_2 ratio lower than 150 mmHg (16). NIV strategies appear safe in mild-to-moderate hypoxemia, whereas HFNC and helmet represent the most promising techniques for first-line treatment of ARDS, but some evidence support IMV for severe cases in order to avoid delayed intubation and increased mortality (17). On the contrary, our study promotes the use of a more conservative approach even in severe ARDS. Early initiation of non-invasive respiratory support and dexmedetomidine can implement oxygenation and match ventilatory demand in spontaneously breathing awake patients, avoiding vigorous inspiratory effort. A more homogeneous distribution of the tidal volume and the alveolar recruitment by a positive end-expiratory pressure protect from lung strain and diaphragm dysfunction. However, spontaneous breathing in patients with lung injury carries the risk of delayed intubation and additional lung damage during the treatment. The phenomenon is described as patient self-inflicted lung injury (P-SILI). This study suggests that the adjunctive administration of dexmedetomidine contributes to contrasting an abnormal pattern of breathing; additionally, a conscious and cooperative sedation, such as what is obtained with this drug, relieves the psychological component of dyspnea and facilitates tolerance. Finally, a minor probability of NIV failure implies preventing intubation, related complications and mortality.

The management of ARDS is very challenging. But respiratory distress does not represent an absolute indication to IMV. Prolonged ventilation means prolonged hospitalization, and increases the risk of tracheostomy, oral feeding, muscle weakness and other complications such as multi-drug resistant infections. This is a very remarkable point since severe COVID-19 causes a persistent dysregulation of immunity. This study remarks the fundamental role of NIV in ARDS. Severe patients can safely undergo NIV in non-intensive care of setting for ARDS, provided with consciousness and with a precise monitoring of failure signals. The sedation with dexmedetomidine modifies the success rate of NIV and is potentially useful in clinical management and decision making.

Regarding the adverse events, liver and kidney function were not involved in relevant consequences even with prolonged infusion of dexmedetomidine. The most common effects are on the cardiovascular system. Hypotension was observed in 12% of DEX group but was as frequent as in the total cohort. Bradycardia was significantly associated with dexmedetomidine (30% of DEX group). The bradycardia was considered serious and the treatment was stopped in 10% of cases. Since bradycardia was observed in 18% of the control group, it is impossible to exclude that other factors or drugs played a part in determining this adverse event.

Limitations

This study has several limitations. First, this is not a multicentric protocol, the data collection was conducted in only one hospital in Naples, even though in one of the most populous cities in Italy. Secondly, the total number of subjects is small. Particularly we collected data from different subsequent waves of COVID-19 regardless for the predominance of different variants and subvariants of the virus. Thirdly, the follow up time is relatively short compared to the natural history of the disease, but it was targeted on the specific

outcome gas exchange which needs to be tested on the short run to correctly manage ARDS. Finally, no definitive recommendations can be made about a single approach but a dynamic evaluation of the single case is to be endorsed to promptly detect the need for endotracheal intubation.

Conclusion

Dexmedetomidine provides a "calm and arousal" status which allows spontaneous ventilation in awake patients treated with NIV and HFNC for COVID-19 related ARDS. The adjunctive therapy with dexmedetomidine is associated with a higher pO_2/FiO_2, lower duration of NIV, and a lower risk of NIV failure. a continuous monitoring of vital signs is recommended to promptly detect anomalies. A higher incidence of sinus bradycardia needs to be considered.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by committee of the University of Campania "Luigi Vanvitelli" and A.O. dei Colli. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FS, AA, and GF: conceptualization and methodology. FS: software and formal analysis. AC, PI, and AM: validation. AC, PI, AIM, RD'A, and AM: investigation. AM, AC, and AIM: resources. PI, AIM, RD'A, and AM: data curation. FS, AC, and AIM: writing. AA, GF, and PI: visualization. AA, GF, and AM: supervision. FS, RD'A, AIM, and PI: project administration. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol*. (2020) 215:108427. doi: 10.1016/j.clim.2020.108427.

2. Available at: https://www.worldometers.info/coronavirus/country/italy/

3. Centers for Disease Control and Prevention. *Underlying medical conditions associated with high risk for severe COVID-19: information for healthcare providers*. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

4. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: a literature review. *Rev Med Virol*. (2021) 31:1–10. doi: 10.1002/rmv.2146

5. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA*. (2005) 294:3124–30. doi: 10.1001/jama.294.24.3124

6. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis. *BMJ*. (2003) 326:185. doi: 10.1136/bmj.326.7382.185

7. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of non-invasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med*. (2007) 35:18–25. doi: 10.1097/01.CCM.0000251821. 44259.F3

8. Radovanovic D, Coppola S, Franceschi E, Gervasoni F, Duscio E, Chiumello DA, et al. Mortality and clinical outcomes in patients with COVID-19 pneumonia treated with non-invasive respiratory support: a rapid review. *J Crit Care*. (2021) 65:1–8. doi: 10.1016/j.jcrc.2021.05.007

9. Procopio G, Cancelliere A, Trecarichi EM, Mazzitelli M, Arrighi E, Perri G, et al. Oxygen therapy via high flow nasal cannula in severe respiratory failure caused by SARS-Cov-2 infection: a real-life observational study. *Ther Adv Respir Dis*. (2020) 14:1753466620963016. doi: 10.1177/1753466620963016

10. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. *Anesth Essays Res*. (2011) 5:128–33. doi: 10.4103/0259-1162.94750

11. Pereira JV, Sanjanwala RM, Mohammed MK, Le ML, Arora RC. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: a systematic review and meta-analysis. *Eur J Anaesthesiol*. (2020) 37:121–31. doi: 10.1097/EJA.0000000000001131

12. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. (1994) 47:1245–51. doi: 10.1016/0895-4356(94)90129-5

13. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet*. (2017) 56:893–913. doi: 10.1007/s40262-017-0507-7.

14. Cruces P, Retamal J, Hurtado DE, Erranz B, Iturrieta P, González C, et al. A physiological approach to understand the role of respiratory effort in the progression of lung injury in SARS-CoV-2 infection. *Crit Care*. (2020) 24:494. doi: 10.1186/s13054-020-03197-7

15. Lewis K, Piticaru J, Chaudhuri D, Basmaji J, Fan E, Møller MH, et al. Safety and efficacy of dexmedetomidine in acutely ill adults requiring non-invasive ventilation: a systematic review and meta-analysis of randomized trials. *Chest*. (2021) 159:2274–88. doi: 10.1016/j.chest.2020.12.052

16. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Non-invasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med*. (2017) 195:67–77. doi: 10.1164/rccm.201606-1306OC

17. Grieco DL, Maggiore SM, Roca O, Spinelli E, Patel BK, Thille AW, et al. Non-invasive ventilatory support and high-flow nasal oxygen as first-line treatment of acute hypoxemic respiratory failure and ARDS. *Intensive Care Med*. (2021) 47:851–66. doi: 10.1007/s00134-021-06459-2

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 02 October 2023
DOI 10.3389/fmed.2023.1244650

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Zhiye Zou,
Shenzhen Second People's Hospital, China
Andrea Glotta,
Ospedale Regionale di Lugano, Switzerland

*CORRESPONDENCE
Vladimir Đurović
✉ vladimir.djurovic@kcv.rs

RECEIVED 22 June 2023
ACCEPTED 18 September 2023
PUBLISHED 02 October 2023

CITATION
Obradović D, Milovančev A, Plećaš Đurić A, Sovilj-Gmizić S, Đurović V, Šović J, Đurđević M, Tubić S, Bulajić J, Mišić M, Jojić J, Pušara M, Lazić I, Đurković M, Bek Pupovac R, Vulić A and Jozing M (2023) High-Flow Nasal Cannula oxygen therapy in COVID-19: retrospective analysis of clinical outcomes – single center experience.
Front. Med. 10:1244650.
doi: 10.3389/fmed.2023.1244650

High-Flow Nasal Cannula oxygen therapy in COVID-19: retrospective analysis of clinical outcomes – single center experience

Dušanka Obradović[1,2], Aleksandra Milovančev[1,3], Aleksandra Plećaš Đurić[1,4], Stanislava Sovilj-Gmizić[2], Vladimir Đurović[5]*, Jovica Šović[6], Miloš Đurđević[6], Stevan Tubić[6], Jelena Bulajić[6], Milena Mišić[6], Jovana Jojić[6], Miroslava Pušara[6], Ivana Lazić[6], Mladen Đurković[6], Renata Bek Pupovac[6], Aleksandra Vulić[6] and Marija Jozing[6]

[1]Faculty of Medicine Novi Sad, University of Novi Sad, Novi Sad, Serbia, [2]Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia, [3]Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia, [4]Clinic of Anesthesiology, Intensive Care and Pain Therapy, University Clinical Center of Vojvodina, Novi Sad, Serbia, [5]Clinic of Nephrology and Clinical Immunology, University Clinical Center of Vojvodina, Novi Sad, Serbia, [6]Urgent Care Center, University Clinical Center of Vojvodina, Novi Sad, Serbia

Background: High-Flow Nasal Cannula (HFNC) oxygen therapy emerged as the therapy of choice in COVID-19-related pneumonia and moderate to severe acute hypoxemic respiratory failure (AHRF). HFNC oxygen therapy in COVID-19 has been recommended based its use to treat AHRF of other etiologies, and studies on assessing outcomes in COVID-19 patients are highly needed. This study aimed to examine outcomes in COVID-19 patients with pneumonia and severe AHRF treated with HFNC.

Materials and methods: The study included 235 COVID-19 patients with pneumonia treated with HFNC. Data extracted from medical records included demographic characteristics, comorbidities, laboratory parameters, clinical and oxygenation status, clinical complications, as well as the length of hospital stay. Patients were segregated into two groups based on their oxygen therapy needs: HDU group, those who exclusively required HFNC and ICU group, those whose oxygen therapy needed to be escalated at some point of hospital stay. The primary outcome was the need for respiratory support escalation (noninvasive or invasive mechanical ventilation) and the secondary outcome was the in-hospital all-cause mortality.

Results: The primary outcome was met in 113 (48%) of patients. The overall mortality was 70%, significantly higher in the ICU group [102 (90.2%) vs. 62 (50.1%), $p < 0.001$]. The rate of intrahospital infections was significantly higher in the ICU group while there were no significant differences in the length of hospital stay between the groups. The ICU group exhibited significant increases in D-dimer, NLR, and NEWS values, accompanied by a significant decrease in the SaO_2/FiO_2 ratio. The multivariable COX proportional regression analysis identified malignancy, higher levels of 4C Mortality Score and NEWS2 as significant predictors of mortality.

Conclusion: High-Flow Nasal Cannula oxygen therapy is a safe type of respiratory support in patients with COVID-19 pneumonia and acute hypoxemic respiratory failure with significantly less possibility for emergence of intrahospital infections. In 52% of patients, HFNC was successful in treating AHRF in COVID-19 patients. Overall, mortality in COVID-19 pneumonia with AHRF is still very high, especially in patients treated with noninvasive/invasive mechanical ventilation.

KEYWORDS

COVID-19, acute hypoxemic respiratory failure, High-Flow Nasal Cannula oxygen therapy, clinical outcomes, intensive care unit

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic changed the pathophysiological insights of many clinical symptoms and signs in the respiratory medicine field, especially relative to the impairment of the gas exchange induced by pneumonia due to the SARS CoV-2 virus (1). Acute hypoxemic respiratory failure (AHRF) was the main reason for hospital admission of patients with COVID-19 pneumonia. The required level of respiratory support depended on the extent of the lung parenchyma involved, comorbidities, and age. The incidence and outcomes of severe COVID-19 associated AHRF are influenced by various factors including indications for hospitalization during different pandemic waves, hospital organization, and available equipment (2, 3).

Early recognition of respiratory support failure is a crucial factor that can significantly impact the outcome of patients with COVID-19 and AHRF. During the COVID-19 pandemic, High Flow Nasal Cannula oxygen therapy (HFNC) was introduced as a noninvasive respiratory support for patients with COVID-19 pneumonia and AHRF. The positive effects of HFNC before the pandemic were first recognized in pediatric population (4). The use of HFNC for respiratory support in adults has been on the rise since the 2000s (5) and it was recommended in the guidelines even before the pandemic era. American College of Physicians (6) and European Society of Intensive Care Medicine (7) recommended the use of HFNC over noninvasive positive pressure ventilation (NIPPV) for treating AHRF. European Respiratory Society released the clinical guidelines for using High-Flow Nasal Cannula in acute respiratory failure implying that it had the advantage over Conventional Oxygen Therapy (COT) and NIPPV (8). In systematic review and meta-analysis (9), which included twenty five randomized clinical trials of patients with AHRF, all studies showed lower risk of intubation when the HFNC was used. In COVID-19, AHRF primarily occurs as a result of ventilation-perfusion shunt. In the majority of cases, this condition manifests clinically and radiologically as acute respiratory distress syndrome (ARDS). The benefits of HFNC in COVID-19 patients with AHRF vary across different studies. For instance, the randomized clinical trial conducted by the Ospina et al. (10) demonstrated advantages of HFNC over COT in terms of reduced intubation incidence and shorter time to recovery. However, the RECOVERY-RS trial (11) found no benefits of HFNC in terms of intubation and mortality rate. Our study aimed to examine HFNC outcomes in COVID-19 patients with pneumonia and severe AHRF.

2. Methodology

2.1. Study population and selection criteria

Our retrospective study included patients admitted to the tertiary-level care University Clinical Centre of Vojvodina at the dedicated COVID facility "Miševuk," from October 2021 to April 2022 with following eligibility criteria: ≥18 years of age, SARS-CoV-2 detected in nasopharyngeal swab using real-time reverse transcription-polymerase chain reaction assay, clinical and radiological signs of pneumonia (bilateral and peripheral ground-glass opacities and consolidations) (12), SpO2 < 94% on room air at sea level, respiratory rate > 30 breaths/min (13) and SaO_2/FiO_2 ratio < 315 mmHg. SaO_2/FiO_2 was used as a surrogate of PaO_2/FiO_2 ratio due to resource limitations, as it was recently proposed as an alternative criterion for acute respiratory distress syndrome (ARDS) (14). This has been supported by several previous studies involving COVID-19 patients with severe AHRF (15–17). The exclusion criteria were: the use of any other respiratory support prior to HFNC, duration of the HFNC less than 24 h; patients with hypercapnic respiratory failure and respiratory acidosis who were treated consequently with NIPPV, those with clinical signs of shock and the ones who required immediate intubation were also excluded. According to the WHO Progression Scale, patients were classified as severe disease with score 6 (13) after a short course of COT (less than 2 h) without achieving the peripheral oxygen saturation ≥ 90% at oxygen flow rate ≥ 15 L/min using a facial mask or non-rebreathing mask and without resolving the signs of respiratory distress.

2.2. Treatment protocol and patient groups

During the abovementioned period, 1,033 patients with COVID-19 pneumonia and acute hypoxemic respiratory failure were admitted to the High Dependency Unit (HDU). HFNC was provided via mechanical ventilators (Prunus Medical Boaray 5000D, Shenzhen, Guangdong, China) using the high-flow oxygen therapy mode. The initial flow rate of 30 to 60 L/min, alongside FiO_2 up to 100%, were subsequently adjusted to achieve a target oxygen saturation of ≥92% while reducing dyspnea and respiratory rate. There were two groups based on their oxygen therapy needs: those who exclusively required HFNC (HDU group) and those whose

oxygen therapy needed to be escalated [NIPPV or invasive mechanical ventilation (IMV)] at some point of hospital stay (ICU group) due to the low SpO_2 levels and signs of respiratory distress (tachypnea, dyspnea, usage of the auxiliary respiratory musculature). All patients were treated with either the standard of care (SOC) therapy or SOC along with baricitinib according to the National Institutes of Health guidelines for treatment of COVID-19 hospitalized patients (13).

2.3. Baseline, clinical, laboratory parameters and outcomes

Data were collected from electronic medical records and included demographic characteristics, comorbidities, vaccinal and smoking status, duration of illness prior to admission and laboratory parameters on admission, as well as the Coronavirus Clinical Characterization Consortium Mortality Score (4C mortality score) (18), neutrophil to lymphocyte ratio (NLR) (19) and National Early Warning Score 2 (NEWS2) (20). For the ICU group, levels of proinflammatory markers, D-dimer, NRL, as well as the values of the NEWS2, were reevaluated shortly prior to the patient's transfer to the ICU. ROX index (21) values were not assessed upon admission due to resource constraints and the absence of an immediate clinical imperative. Instead, ROX index evaluation was conducted only before the patient's transfer to the ICU when it became clinically relevant. We have also collected the data on frequency of intrahospital infections, pneumothorax/pneumomediastinum, pulmonary embolism, and the length of hospital stay. The primary outcome was defined as HFNC failure with the need for respiratory support escalation which included either noninvasive or invasive mechanical ventilation. The secondary outcome was the in-hospital all-cause mortality. The study protocol was approved by the Ethics Committee of the University Clinical Centre of Vojvodina (protocol code: 00-39, date of approval: 9 February 2023).

2.4. Statistical analysis

The normality of the continuous variables was assessed using the Kolmogorov–Smirnov test. Non-normally distributed continuous variables were reported as the median with the interquartile range (Q1-Q3). Continuous variables were compared between independent groups using the Wilcoxon rank-sum test, while paired samples were analyzed using the paired Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Cox proportional hazards modeling was used to examine the association between the outcomes and predictor variables. Hazard ratios (HR) and their 95% confidence intervals (CI) were reported to quantify the magnitude and direction of the associations. Kaplan–Meier curves were used to visualize survival probabilities, stratified by relevant variables. All statistical tests were two-tailed and the alpha level of 0.05 was set as a significance threshold. No imputations were used for the missing data. Statistical analyses were conducted using RStudio 2023.03.1 + 446 "Cherry Blossom" Release.

3. Results

3.1. Baseline patients' characteristics

Our study included 235 patients treated with HFNC (Figure 1). The median age was 70 years (62–79) with 58.3% of males. Hypertension was the most common comorbidity, observed in 67.7%, with 10.6% smokers. The group of patients without the progression of respiratory failure were significantly older [72 years (61–84) vs. 70 (63–75), respectively, $p = 0.022$]. There were no significant differences in the prevalence of comorbidities between the two groups, nor were there any significant differences regarding vaccination status. Table 1 provides an overview of the baseline characteristics of the patients at hospital admission. There were also no significant differences in admission parameters between groups as shown in Table 2.

3.2. Intrahospital events and treatment measures

Among the patients included in the study, 18.7% acquired intrahospital infections during their hospital stay. The incidence of intrahospital infections was significantly higher in the group of patients who required non-invasive ventilation or mechanical ventilation [30 (26.5%) vs. 14 (11.5%) $p = 0.003$]. Specifically, patients in this group had a higher prevalence of urinary tract infections [16 (14.2%) vs. 3 (2.5%), $p = 0.001$] and intrahospital pneumonia was exclusively observed in this group [18 (15.9), $p < 0.001$] (Table 3). There were no significant differences between the two groups in terms of corticosteroid therapy, the use of baricitinib, or the occurrence of pulmonary thromboembolism, pneumothorax, and pneumomediastinum (Table 4).

3.3. Clinical course and outcomes

Patients who were transferred to the ICU did not exhibit a significant change in CRP and PCT levels. However, significant increases were observed in D-dimer, NLR, and NEWS2 values. Additionally, there was a significant decrease in SaO_2/FiO_2 ratio, reflecting worsening oxygenation. The median ROX score at the ICU transfer was 3.40 (2.80–4.55) as shown in Table 5.

3.3.1. Primary outcome

HFNC failure was observed in 113 patients (48%) with 96 of them (85%) initially receiving noninvasive ventilation. Among the participants who initially received noninvasive ventilation, 75 of them (78%) required subsequent mechanical ventilation. Patients that were placed in the ICU received HFNC oxygen therapy for the significantly shorter amount of time (2 days vs. 12 days, $p < 0.001$).

3.3.2. Secondary outcome

Regarding the secondary outcome, which was observed in 164 patients (70%), a significantly higher mortality rate was reported in the ICU compared to the HDU group [102 (90%) vs. 62 (51%), $p < 0.001$]. The length of hospital stay did not differ significantly between the two groups as shown in Table 6. The HDU group

10.3389/fmed.2023.1244650

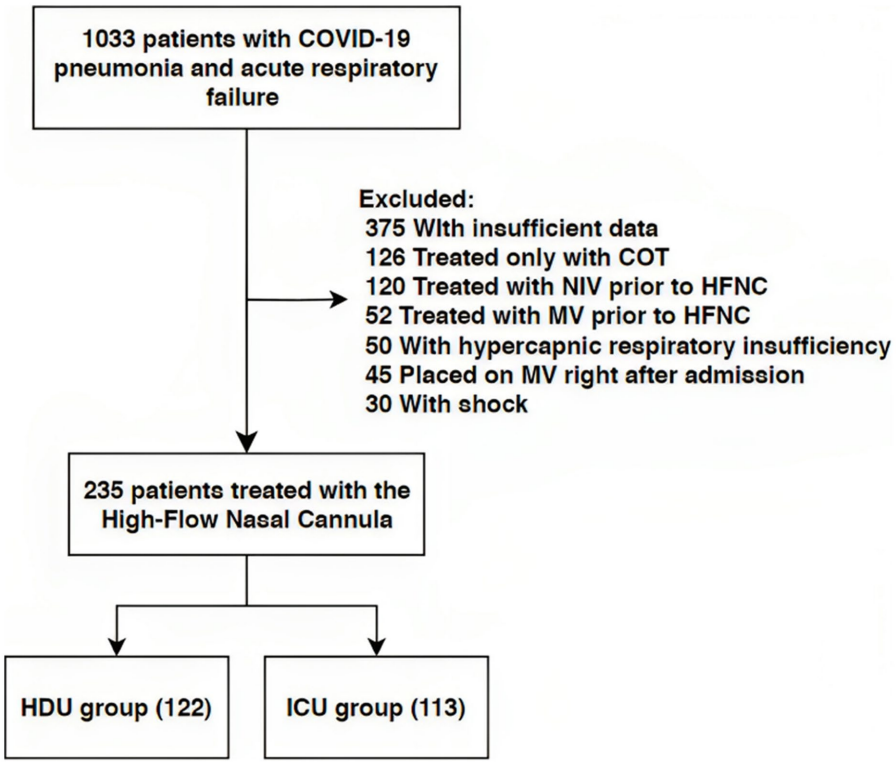


FIGURE 1
Flow chart of patient selection. NIV, Non-Invasive Ventilation; HFNC, High Flow Nasal Cannula; MV, Mechanical Ventilation; HDU, High Dependency Unit; ICU, Intensive Care Unit.

TABLE 1 Patients' characteristics at the admission.

Parameter[1]	Overall, $N = 235$[2]	HDU, $N = 122$[2]	ICU, $N = 113$[2]	p[3]
Sex (*M*)	137 (58.3)	72 (59)	65 (57.5)	0.816
Age	70 (62–79)	72 (61–84)	70 (63–75)	**0.022**
Disease duration prior to admission (days)	8 (2–7)	7 (5–10)	8 (5–10)	0.691
Disease duration before the diagnosis (days)	5 (2–7)	4 (2–6)	5 (3–8)	**0.043**
Vaccinated	64 (27.2)	35 (28.7)	29 (25.7)	0.603
Smoker	25 (10.6)	13 (10.7)	12 (10.6)	0.993
Comorbidities				
Hypertension	159 (67.7)	83 (68.0)	76 (67.3)	0.899
Diabetes	75 (31.9)	37 (30.3)	38 (33.6)	0.588
Obesity	52 (22.1)	21 (17.2)	31 (22.4)	0.059
Cardiomyopathy	27 (11.5)	15 (12.3)	12 (10.6)	0.687
Atrial fibrillation	13 (5.5)	7 (5.7)	6 (5.3)	0.886
COPD	17 (7.2)	9 (7.4)	8 (7.1)	0.930
Asthma	14 (6.0)	5 (4.1)	9 (8.0)	0.211
CKD	13 (5.5)	9 (7.4)	4 (3.5)	0.199
History of stroke	13 (5.5)	8 (6.6)	5 (4.4)	0.475
Malignancy	24 (10.2)	16 (13.1)	8 (7.1)	0.127

[1]COPD, Chronic obstructive pulmonary disease; CKD, Chronic kidney disease.
[2]Median (Q1–Q3)/*n* (%).
[3]Wilcoxon rank sum test; Pearson's Chi-squared test.

TABLE 2 Admission parameters.

Parameter[1]	Overall, $N = 235$[2]	HDU, $N = 122$[2]	ICU, $N = 113$[2]	p[3]
CRP (mg/L)	130 (74–190)	132 (61–206)	121 (81–176)	0.969
PCT (ng/mL)	0.19 (0.09–0.37)	0.18 (0.08–0.34)	0.21 (0.11–0.53)	0.140
D-dimer (mg/L)	1.6 (1.0–3.2)	1.7 (1.0–4.3)	1.5 (0.9–2.7)	0.132
ALT (IU/L)	37 (24–56)	34 (22–55)	41 (27–59)	0.131
AST (IU/L)	48 (35–73)	46 (35–69)	51 (36–76)	0.414
GGT (IU/L)	53 (32–87)	52 (30–86)	56 (35–87)	0.551
Leukocyte count ($\times 10^9$)	8.7 (6.4–12.3)	8.7 (6.8–12.6)	8.7 (6.1–11.8)	0.399
Lymphocyte count ($\times 10^9$)	0.73 (0.48–1.03)	0.75 (0.47–1.05)	0.70 (0.48–1.01)	0.817
Neutrophil count ($\times 10^9$)	7.3 (5.1–10.4)	7.3 (5.6–10.5)	7.2 (4.7–10.1)	0.411
Thrombocyte count ($\times 10^9$)	194 (145–268)	203 (153–271)	182 (141–255)	0.160
Erythrocyte count ($\times 10^{12}$)	4.73 (4.27–5.12)	4.77 (4.26–5.15)	4.64 (4.27–5.12)	0.405
Hemoglobin (g/L)	134 (123–147)	135 (123–147)	133 (123–148)	0.914
SaO_2/FiO_2	1.19 (0.99–1.58)	1.17 (1.00–1.58)	1.34 (0.98–1.58)	0.586
NLR	9 (6–17)	9 (6–18)	10 (5–16)	0.686
NEWS2	6 (4–8)	6 (4–8)	6 (4–7)	0.530
4C Mortality Score	13 (10–15)	13 (10–15)	13 (10–15)	0.647

[1]CRP, C-reactive protein; PCT, Procalcitonin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma glutamyl transferase; NLR, Neutrophil-to-Lymphocyte Ratio; NEWS2, National Early Warning Score 2; 4C Mortality score, Coronavirus Clinical Characterization Consortium Mortality Score.
[2]Median (Q1–Q3).
[3]Wilcoxon rank sum test.

TABLE 3 Intrahospital infections.

Parameter	Overall, $N = 235$[1]	HDU, $N = 122$[1]	ICU, $N = 113$[1]	p[2]
Intrahospital infections	44 (18.7)	14 (11.5)	30 (26.5)	**0.003**
Urinary tract infection	19 (8.1)	3 (2.5)	16 (14.2)	**0.001**
Clostridium difficile Infection	20 (8.5)	13 (10.7)	7 (6.2)	0.221
Intrahospital pneumonia	18 (7.7)	0 (0)	18 (15.9)	< **0.001**

[1]*n* (%).
[2]Pearson's Chi-squared test; Fisher's exact test.

TABLE 4 Treatment and complications.

Therapy/complication	Overall, $N = 235$[1]	HDU, $N = 122$[1]	ICU, $N = 113$[1]	p[2]
Corticosteroids	227 (96.6)	115 (94.3)	112 (99.1)	0.067
Baricitinib	33 (14.0)	19 (15.6)	14 (12.4)	0.483
Pulmonary thromboembolism	22 (9.4)	11 (9.0)	11 (9.7)	0.850
Pneumothorax	12 (5.1)	6 (4.9)	6 (5.3)	0.892
Pneumomediastinum	13 (5.5)	4 (4.1)	8 (7.1)	0.318

[1]*n* (%).
[2]Pearson's Chi-squared test.

exhibited a significantly better survival compared to the ICU group, with a hazard ratio (HR) of 0.56 (95% CI 0.40–0.77, $p < 0.001$), as demonstrated in Figure 2.

In the multivariable Cox proportional hazard analysis for the secondary outcome, vaccinal status (HR 0.7, 95% CI 0.49–1.02) and the intrahospital use of baricitinib (HR 0.43, 95% CI 0.23–0.79) emerged as the negative predictors of mortality. On the other hand, malignancy posed as the strongest positive mortality predictor with HR of 2.14 (95% CI 1.33–3.43). The significant indicators of the secondary outcome were also the higher levels of 4C mortality score and NEWS2 (Figure 3).

4. Discussion

Our retrospective study, focused on COVID-19 patients with AHRF that were treated with HFNC oxygen therapy, was performed during the fifth and sixth pandemic wave in Serbia with Delta and

TABLE 5 Laboratory parameters' progression in the ICU group.

Parameter[1]	At admission, $N = 113$[2]	Transfer to the ICU, $N = 113$[2]	p[3]
CRP	121 (81–176)	117 (72–173)	0.683
PCT	0.21 (0.11–0.53)	0.21 (0.11–0.78)	0.288
D-dimer	1.53 (0.92–2.70)	2.07 (1.26–4.30)	**0.019**
NLR	10 (5–10)	14 (9–23)	**<0.001**
NEWS2	6 (4–7)	8 (6–10)	**<0.001**
SaO_2/FiO_2	1.34 (0.98–1.58)	0.94 (0.88–1.03)	**<0.001**
ROX index	–	3.40 (2.80–4.55)	–

[1]CRP, C-Reactive Protein; PCT, Procalcitonin; NLR, Neutrophil-to-Lymphocyte Ratio; NEWS2, National Early Warning Score 2.
[2]Median (Q1–Q3).
[3]Wilcoxon signed rank test with continuity correction.

TABLE 6 Clinical course and outcomes.

Parameter[1]	Overall, $N = 235$[2]	HDU, $N = 122$[2]	ICU, $N = 113$[2]	p[3]
Length of hospital stay (days)	11 (7–20)	12 (5–22)	11 (8–16)	0.877
All-cause mortality	164 (69.7)	62 (50.1)	102 (90.2)	**<0.001**

[1]HFNC, High Flow Nasal Cannula.
[2]Median (Q1–Q3)/*n* (%).
[3]Wilcoxon rank sum test; Pearson's Chi-squared test.

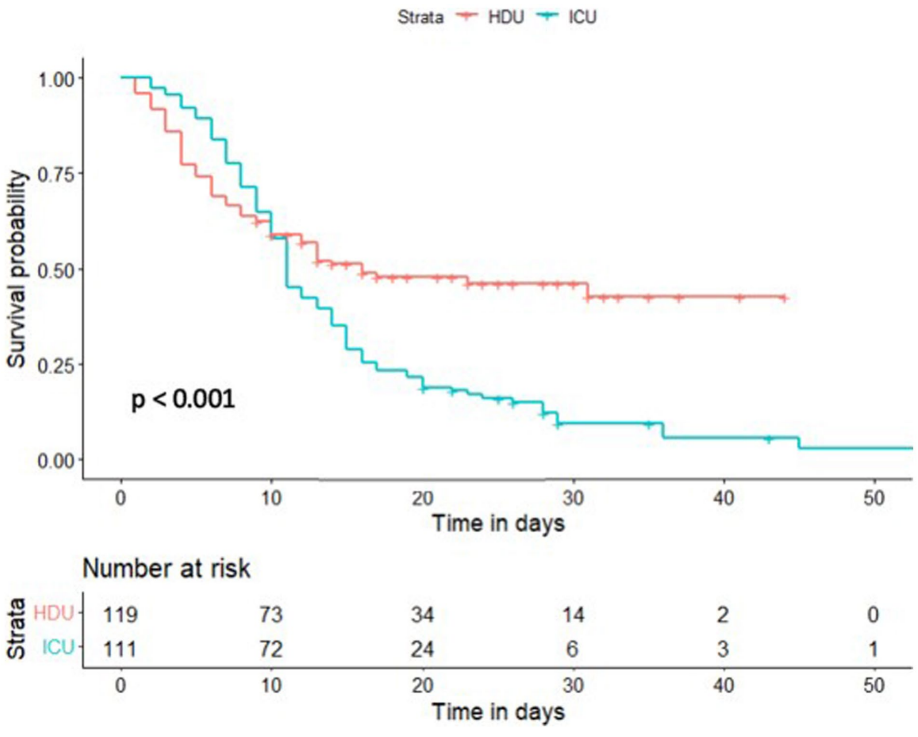


FIGURE 2
Kaplan–Meier estimate of survival of High Flow Nasal Cannula (HFNC) treated patients stratified by the primary outcome. HDU, High Dependency Unit; ICU, Intensive Care Unit.

Omicron SARS-CoV-2 variants (22). The main findings in our study were as follows: (1) Our cohort consisted mostly of patients with the median age of 70 years, and hypertension as the most common comorbidity; (2) HFNC was successful in improving clinical course in 52% of patients; (3) The all-cause in-hospital mortality rate was high, reaching 70%, and it was significantly higher (90%) in patients with who experienced HFNC failure; (4) Patients treated with baricitinib showed significantly better survival; (5) Patients with concomitant

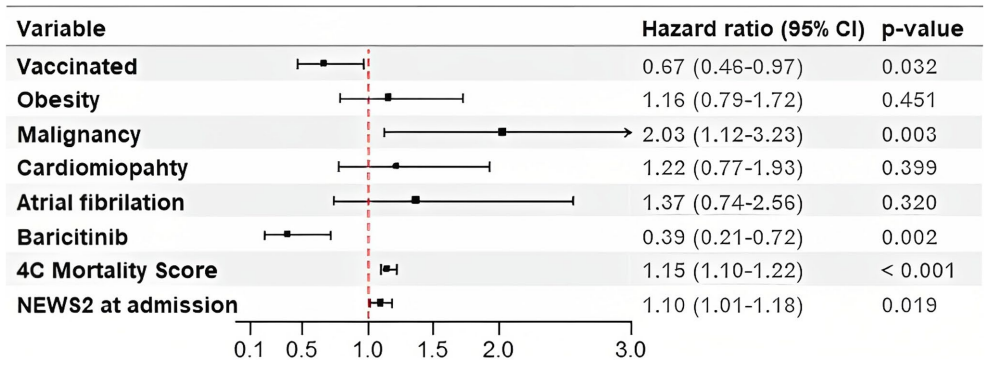


FIGURE 3
Hazard Ratios for the Secondary Outcome in patients with acute respiratory failure treated with High-Flow Nasal Cannula. 4C Mortality Score, Coronavirus Clinical Characterization Consortium Mortality Score; NEWS2, National Early Warning Score 2.

malignant disease had a significantly worse prognosis. Previous retrospective studies at the beginning of the pandemic showed high mortality rates from 36% (23) among the older COVID-19 patients with AHRF who were treated with invasive mechanical ventilation up to the 62% as one Chinese study reported (24). As the pandemic progressed, the demand for ICU beds often exceeded hospitals' capacities, leading to the conversion of non-ICU spaces to ICU units (25). The scarcity of ICU beds in many countries required alternative respiratory support for patients with AHRF, primarily focusing on HFNC, with the main goal being avoidance of intubation. The results the SOHO COVID trial (26) showed a clear advantage of HFNC to COT which was reflected in significantly lower intubation rate in the HFNC group compared to the COT group.

In our study, the majority of baseline characteristics, laboratory findings and oxygenation status were similar between two groups, except for the age in favor of the HDU group (72 vs. 70 years) and the disease duration prior to the diagnosis establishment with the median in ICU group being 5 vs. 4 days in the HDU group, $p = 0.043$. Similar findings have been reported in the cohort retrospective study from England from the beginning of the pandemic, where the timing of hospital admission was associated with poorer clinical outcomes in patients with COVID-19 (27). The most frequent comorbidities in our study group were hypertension, diabetes and obesity which is consistent with findings from other studies (28, 29). The patients in the ICU group were more obese, but without reaching the statistical significance. There were no significant differences regarding the baseline laboratory parameters, NEWS2, 4C mortality score and SaO_2/FiO_2 ratio between groups.

Among the individuals included in our study, 18.7% of them acquired intrahospital infections during their hospital stay with the incidence being significantly higher in the ICU group. Our results are similar with the results of the review of secondary pulmonary bacterial infections among the patients with COVID-19 pneumonia (30), showing the low incidence in general, but higher in ICU patients. In our study, the intrahospital pneumonia was observed exclusively in ICU group with higher prevalence of urinary tract infections (UTI). In the single-center retrospective study of COVID-19 patients during the first pandemic wave (31), secondary infections were present in 7.3% of times. The most common intrahospital infections were ventilator associated pneumonia (VAP) and UTI which is also comparable to our study. On the other hand, the European multicenter study focusing on VAP in patients that spent more than 48 h on mechanical ventilation reported slightly higher incidence of VAP, 36.1% (32). The absence of significant differences in baseline parameters and the frequency of corticosteroid and baricitinib usage suggests that it is reasonable to consider that the higher frequency of intrahospital infections in the ICU group could be due to a more rapid disease progression in these patients. The accelerated progression of the disease in the ICU group may have led to increased susceptibility to infections and the need for higher levels of respiratory support, ultimately contributing to the observed differences. Regarding the other analyzed clinical complications (thromboembolism, pneumothorax, and pneumomediastinum), no differences were reported among the groups.

The failure of non-invasive respiratory support that includes both HFNC and NIPPV, in patients with AHRF is directly related to delayed intubation and consequently higher mortality rate. Before the COVID-19 era, studies such as LUNG SAFE (33) demonstrated that the NIPPV in patients with severe AHRF and ARDS was linked to a significantly higher mortality rate compared to IMV (36.2% vs. 24.7%, respectively). FLORALI study (34), however, showed the advantage of HFNC utilization in comparison to the COT, where HFNC group exhibited significantly lower intubation rate. In the early phase of the COVID-19 pandemic, the recommendations were in favor of the early intubation, mostly due to the pronounced patient self-induced lung injury (P-SILI) and the higher mortality rate associated with the delayed intubation (35). Longer duration of the non-invasive respiratory support before the ICU admission has been identified as an independent risk factor of in-hospital mortality (36). Contrary to these findings, in our study, the overall duration of HFNC was 4 days, with a significant difference observed between HDU and ICU group (12 vs. 2 days, respectively, $p < 0.001$). Timely recognition of the non-invasive respiratory support failure is of the high importance. Studies have reported incidence of the NIPPV failure associated mortality ranging from 26.5% (37) to 49.6% (38). In our study, primary outcome, defined as the HFNC failure, was observed in 113 patients, most of whom (85%) initially received NIPPV prior to the ICU transfer and 78% of patients treated with NIPPV required subsequent mechanical ventilation.

Patients transferred to the ICU did not exhibit significant changes in CRP and PCT levels. However, significant increases were observed

in D-dimer levels, as well as NLR and NEWS2 values. Additionally, there was a significant decrease in SaO2/FiO2 ratio, reflecting worsening oxygenation. The median ROX score at the ICU transfer was 3.40 (2.80–4.55). Our findings are comparable with the single-center study conducted by Talpoș et al. where the PaO_2/FiO_2 and ROX score emerged as the HFNC failure predictor (39).

The study from Jordan (40) reported a mortality rate of 23% during the early period of the pandemic, while Wuhan (41) reported a rate of 32%. Similarly, in a multicentre Italian study, which was also conducted during the early stages of the pandemic (36), the mortality rate increased to 43% following the NIPPV failure. Additionally, in New York (25), the mortality rate reached 61% after intubation. The overall in-hospital mortality rate in our study was high, reaching 70%, with a significantly more deaths reported in the ICU group (51% vs. 90%, $p < 0.001$, respectively). The survival analysis using Kaplan–Meier estimate reported the significantly better survival in the HDU group with a hazard ratio (HR) of 0.56 (95% CI 0.40–0.77, $p < 0.001$). The inclusion of severely ill patients with multiple comorbidities and a median age of 70 years could explain such a high mortality rate in our study group. The literature data shows that the progression to more severe COVID-19 disease is associated with higher age (≥50 years, with risk increasing substantially at ages over 65 years), race/ethnicity, as well as the presence of an underlying medical conditions (42–44).

The treatment protocols for COVID-19 have evolved during the pandemic, introducing new anti-inflammatory and antiviral drugs. Several randomized trials such as ACCT-2 and COV-BARRIER studies (45, 46) showed some promising results of baricitinib in terms of recovery time and reduction of mortality rates which is why the National Institutes of Health (NIH) Treatment Guidelines Panel has recommended the use of baricitinib in patients with rapidly increasing needs for higher respiratory support (13). The baricitinib was administered to 33 patients in our study, and 19 of them were successfully treated with HFNC. The use of baricitinib was associated with the better survival (HR 0.39, 95% CI 0.21–0.72) in the multivariate COX proportional analysis when adjusted for other covariates. These findings are consistent with the results of the COV-BARRIER study (46), A retrospective single-center study (47) comparing outcomes in patients treated with HFNC also reported a significantly lower 28-day all-cause mortality rate in patients treated with baricitinib compared to the standard care group. The vaccinal status is well known as a predictor of outcomes in patients with COVID 19 (48–50), and in our study, it also emerged as a significant negative predictor of mortality. We observed the similar vaccination rate between groups (27.2% in HDU vs. 28.7% in ICU group) and the vaccinated individuals had 30% reduced mortality rate compared to the non-vaccinated (HR 0.67, 95% CI 0.46–0.97). Similar results have been reported in a large retrospective study from the USA (49) where the proportion of unvaccinated individuals was also high (73.7%) with significantly higher mortality rate in unvaccinated group.

COVID 19 related mortality in patients with cancer is higher than in those without malignancy. According to a study on the impact of solid cancer on in-hospital mortality in COVID-19 patients, the 30-day in-hospital mortality rate was found to be higher in patients with solid cancer (31.7%) compared to those without cancer (20.0%) (51). Cancer not only serves as an independent risk factor for the COVID-19 disease severity (51), but also increases the risk of mortality (52). The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) reported a significant difference in mortality rates between cancer and non-cancer patients (40.5% vs. 28.5%, respectively) (53). In our study, malignancy was observed to be the strongest positive predictor of intrahospital mortality with HR of 2.03 (95% CI 1.12–3.23). Additionally, the 4C Mortality Score and NEWS 2 score were identified as significant predictors of all-cause in-hospital mortality. The 4C score was proven to be one of the validated scoring systems for mortality prediction in COVID-19. It exhibits relatively high positive predictive value (62%) for mortality when it is over 15 (range 0–21) (53). In our study, the median 4C Mortality Score was 13 (10–15) in both groups and in a multivariable COX proportional analysis the HR of 1.15 (1.09–1.21) was observed. The median NEWS2 score at admission was also equal in both groups, 6 (4–8) vs. 6 (4–7), with the significant increase among patients transferred to the ICU, 8 (6–10), $p < 0.001$. A retrospective study from Romania (54) compared the predictive value of the 4C Mortality score, NEWS score, and CURB-65 score, with the NEWS score showing the best predictive power. In another study (55), the performance evaluation of NEWS and NEWS2 in predicting two outcomes (death and ICU admission) showed higher predictive power of scores for COVID-19 positive patients compared to those without COVID-19 detected.

This study has several limitations. Although the big number of patients' data were processed, the study had a retrospective character and therefore, it possesses all of the limitations of a retrospective study. The study was also single-centered and we did not have a control group that could be used for a comparison. Finally, factors such as age, number of comorbidities, severity of the disease etc. could have had an impact on the abovementioned outcomes.

5. Conclusion

Our study is a contribution to the recommendations for application of HFNC in patients who fulfilled the criteria of severe COVID-19 pneumonia at the admission. The mortality rate in patients treated with HFNC failure is closely related to the comorbidity presence, clinical status of the patients and vaccinal status. In 52% of patients, HFNC was successful in treating AHRF in severe COVID-19 pneumonia.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of the University Clinical Centre of Vojvodina (protocol code: 00-39, date of approval: 9 February 2023). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

DO and APĐ contributed to the conceptualization and design of the study. DO, APĐ, and JŠ organized the database. SS-G, JŠ, MiĐ, ST, JB, MM, JJ, MP, IL, MlĐ, RBP, AV, and MJ collected the data. VĐ performed the statistical analysis. DO, VĐ, and AM wrote sections of the manuscript. AM conducted the supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

Acknowledgments

The authors would like to acknowledge all the healthcare professionals that were included in the treatment of the patients included in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Gattinoni L, Gattarello S, Steinberg I, Busana M, Palermo P, Lazzari S, et al. COVID-19 pneumonia: pathophysiology and management. *Eur Respir Rev*. (2021) 30:210138. doi: 10.1183/16000617.0138-2021

2. Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. *Eur Respir J*. (2021) 57:2100048. doi: 10.1183/13993003.00048-2021

3. Dondorp AM, Hayat M, Aryal D, Beane A, Schultz MJ. Respiratory support in COVID-19 patients, with a focus on resource-limited settings. *Am J Trop Med Hyg*. (2020) 102:1191–7. doi: 10.4269/ajtmh.20-0283

4. Shoemaker MT, Pierce MR, Yoder BA, DiGeronimo RJ. High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol*. (2007) 27:85–91. doi: 10.1038/sj.jp.7211647

5. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth*. (2009) 103:886–90. doi: 10.1093/bja/aep280

6. Qaseem A, Etxeandia-Ikobaltzeta I, Fitterman N, Williams JW, Kansagara D, Clinical Guidelines Committee of the American College of Physicians, et al. Appropriate use of high-flow nasal oxygen in hospitalized patients for initial or postextubation management of acute respiratory failure: a clinical guideline from the American College of Physicians. *Ann Intern Med*. (2021) 174:977–84. doi: 10.7326/M20-7533

7. Rochwerg B, Einav S, Chaudhuri D, Mancebo J, Mauri T, Helviz Y, et al. The role for high flow nasal cannula as a respiratory support strategy in adults: a clinical practice guideline. *Intensive Care Med*. (2020) 46:2226–37. doi: 10.1007/s00134-020-06312-y

8. Oczkowski S, Ergan B, Bos L, Chatwin M, Ferrer M, Gregoretti C, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J*. (2022) 59:2101574. doi: 10.1183/13993003.01574-2021

9. Ferreyro BL, Angriman F, Munshi L, Del Sorbo L, Ferguson ND, Rochwerg B, et al. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA*. (2020) 324:57–67. doi: 10.1001/jama.2020.9524

10. Ospina-Tascón GA, Calderón-Tapia LE, García AF, Zarama V, Gómez-Álvarez F, Álvarez-Saa T, et al. Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial. *JAMA*. (2021) 326:2161–71. doi: 10.1001/jama.2021.20714

11. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. *JAMA*. (2022) 327:546–58. doi: 10.1001/jama.2022.0028

12. Churruca M, Martínez-Besteiro E, Couñago F, Landete P. COVID-19 pneumonia: a review of typical radiological characteristics. *World J Radiol*. (2021) 13:327–43. doi: 10.4329/wjr.v13.i10.327

13. COVID-19 Treatment Guidelines [Internet]. []. *Information on COVID-19 treatment, prevention and research*. Available at: https://www.covid19treatmentguidelines.nih.gov

14. Wick KD, Matthay MA, Ware LB. Pulse oximetry for the diagnosis and management of acute respiratory distress syndrome. *Lancet Respir Med*. (2022) 10:1086–98. doi: 10.1016/S2213-2600(22)00058-3

15. Bonaventura A, Mumoli N, Mazzone A, Colombo A, Evangelista I, Cerutti S, et al. Correlation of SpO2/FiO2 and PaO2/FiO2 in patients with symptomatic COVID-19: an observational, retrospective study. *Intern Emerg Med*. (2022) 17:1769–75. doi: 10.1007/s11739-022-02981-3

16. Zaccagnini G, Berni A, Pieralli F. Correlation of non-invasive oxygenation parameters with pa O2/FiO2 ratio in patients with COVID-19 associated ARDS. *Eur J Intern Med*. (2022) 96:117–9. doi: 10.1016/j.ejim.2021.12.015

17. Kumar A, Aggarwal R, Khanna P, Kumar R, Singh AK, Soni KD, et al. Correlation of the SpO2/FiO2 (S/F) ratio and the PaO2/FiO2 (P/F) ratio in patients with COVID-19 pneumonia. *Med Intensiva*. (2022) 46:408–10. doi: 10.1016/j.medin.2021.10.005

18. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C mortality score. *BMJ*. (2020) 370:m3339. doi: 10.1136/bmj.m3339

19. Takada T, Hoogland J, Yano T, Fujii K, Fujiishi R, Miyashita J, et al. Added value of inflammatory markers to vital signs to predict mortality in patients suspected of severe infection. *Am J Emerg Med*. (2020) 38:1389–95. doi: 10.1016/j.ajem.2019.11.030

20. RCP London [Internet]. (2020). *NEWS2 and deterioration in COVID-19*. Available at: https://www.rcplondon.ac.uk/news/news2-and-deterioration-covid-19 (Accessed June 22, 2023)

21. Zhou X, Liu J, Pan J, Xu Z, Xu J. The ROX index as a predictor of high-flow nasal cannula outcome in pneumonia patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *BMC Pulm Med*. (2022) 22:121. doi: 10.1186/s12890-022-01914-2

22. Medić S, Anastassopoulou C, Lozanov-Crvenković Z, Vuković V, Dragnić N, Petrović V, et al. Risk and severity of SARS-CoV-2 reinfections during 2020-2022 in Vojvodina, Serbia: a population-level observational study. *Lancet Reg Health Eur*. (2022) 20:100453. doi: 10.1016/j.lanepe.2022.100453

23. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region. *JAMA*. (2020) 323:1574–81. doi: 10.1001/jama.2020.5394

24. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. (2020) 8:475–81. doi: 10.1016/S2213-2600(20)30079-5

25. Nishikimi M, Jafari D, Singh N, Shinozaki K, Sison CP, Shoaib M, et al. Mortality of mechanically ventilated COVID-19 patients in traditional versus expanded intensive care units in New York. *Ann Am Thorac Soc*. (2022) 19:1346–54. doi: 10.1513/AnnalsATS.202106-705OC

26. Frat JP, Quenot JP, Badie J, Coudroy R, Guitton C, Ehrmann S, et al. Effect of high-flow nasal cannula oxygen vs standard oxygen therapy on mortality in patients with respiratory failure due to COVID-19: the SOHO-COVID randomized clinical trial. *JAMA*. (2022) 328:1212–22. doi: 10.1001/jama.2022.15613

27. Alaa A, Qian Z, Rashbass J, Benger J, van der Schaar M. Retrospective cohort study of admission timing and mortality following COVID-19 infection in England. *BMJ Open*. (2020) 10:e042712. doi: 10.1136/bmjopen-2020-042712

28. Russell CD, Lone NI, Baillie JK. Comorbidities, multimorbidity and COVID-19. *Nat Med*. (2023) 29:334–43. doi: 10.1038/s41591-022-02156-9

29. Amin R, Sohrabi MR, Zali AR, Hannani K. Five consecutive epidemiological waves of COVID-19: a population-based cross-sectional study on characteristics, policies, and health outcome. *BMC Infect Dis*. (2022) 22:906. doi: 10.1186/s12879-022-07909-y

30. Chong WH, Saha BK, Ramani A, Chopra A. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. *Infection*. (2021) 49:591–605. doi: 10.1007/s15010-021-01602-z

31. Chan L, Gupta S, Sacco AJ, Kasule SN, Chaffin H, Feller FF, et al. Infections and antimicrobial prescribing in patients hospitalized with coronavirus disease 2019 (COVID-19) during the first pandemic wave. *Antimicrob Steward Healthc Epidemiol*. (2023) 3:e75. doi: 10.1017/ash.2023.135

32. Rouzé A, Martin-Loeches I, Povoa P, Makris D, Artigas A, Bouchereau M, et al. Relationship between SARS-CoV-2 infection and the incidence of ventilator-associated lower respiratory tract infections: a European multicenter cohort study. *Intensive Care Med*. (2021) 47:188–98. doi: 10.1007/s00134-020-06323-9

33. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med*. (2017) 195:67–77. doi: 10.1164/rccm.201606-1306OC

34. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. (2015) 372:2185–96. doi: 10.1056/NEJMoa1503326

35. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists. *Anaesthesia*. (2020) 75:785–99. doi: 10.1111/anae.15054

36. Boscolo A, Pasin L, Sella N, Pretto C, Tocco M, Tamburini E, et al. Outcomes of COVID-19 patients intubated after failure of non-invasive ventilation: a multicenter observational study. *Sci Rep*. (2021) 11:17730. doi: 10.1038/s41598-021-96762-1

37. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. *Eur Respir J*. (2020) 56:2001935. doi: 10.1183/13993003.01935-2020

38. Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med*. (2020) 8:853–62. doi: 10.1016/S2213-2600(20)30316-7

39. Talpoș MT, Rasson A, De Terwangne C, Simonet O, Taccone FS, Vallot F. Early prediction of high-flow oxygen therapy failure in COVID-19 acute hypoxemic respiratory failure: a retrospective study of scores and thresholds. *Cureus*. (2022) 14:e32087. doi: 10.7759/cureus.32087

40. Al Oweidat K, Al-Amer R, Saleh MY, Albtoosh AS, Toubasi AA, Ribie MK, et al. Mortality, intensive care unit admission, and intubation among hospitalized patients with COVID-19: a one-year retrospective study in Jordan. *J Clin Med*. (2023) 12:2651. doi: 10.3390/jcm12072651

41. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. (2020) 146:110–8. doi: 10.1016/j.jaci.2020.04.006

42. Pennington AF, Kompaniyets L, Summers AD, Danielson ML, Goodman AB, Chevinsky JR, et al. Risk of clinical severity by age and race/ethnicity among adults hospitalized for COVID-19-United States, 2020. Open forum. *Infect Dis*. (2021) 8:ofaa 638. doi: 10.1093/ofid/ofaa638

43. Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al. Underlying medical conditions and severe illness among 540, 667 adults hospitalized with COVID-19, 2020–2021. *Prev Chronic Dis*. (2021) 18:E66. doi: 10.5888/pcd18.210123

44. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx. *New York Metabolism*. (2020) 108:154262. doi: 10.1016/j.metabol.2020.154262

45. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. (2021) 384:795–807. doi: 10.1056/NEJMoa2031994

46. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. (2021) 9:1407–18. doi: 10.1016/S2213-2600(21)00331-3

47. Obradović D, Popović M, Banjac M, Bulajić J, Đurović V, Urošević I, et al. Outcomes in COVID-19 patients with pneumonia treated with high-flow oxygen therapy and baricitinib—retrospective single-center study. *Life*. (2023) 13:755. doi: 10.3390/life13030755

48. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–2021. *Lancet*. (2022) 399:1513–36. doi: 10.1016/S0140-6736(21)02796-3

49. Baker TB, Bolt DM, Smith SS, Piasecki TM, Conner KL, Bernstein SL, et al. The relationship of COVID-19 vaccination with mortality among 86, 732 hospitalized patients: subpopulations, patient factors, and changes over time. *J Gen Intern Med*. (2023) 38:1248–55. doi: 10.1007/s11606-022-08007-0

50. Centers for Disease Control and Prevention [Internet]. *COVID data tracker weekly review*. (2022). Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/past-reports/04222022.html (Accessed June 22, 2023)

51. de Azambuja E, Brandão M, Wildiers H, Laenen A, Aspeslagh S, Fontaine C, et al. Impact of solid cancer on in-hospital mortality overall and among different subgroups of patients with COVID-19: a nationwide, population-based analysis. *ESMO Open*. (2020) 5:e000947. doi: 10.1136/esmoopen-2020-000947

52. Jani CT, Schooley RT, Mckay RR, Lippman SM. Cancer, more than a "COVID-19 co-morbidity". *Front Oncol*. (2023) 13:1107384. doi: 10.3389/fonc.2023.1107384

53. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. (2020) 369:m1985. doi: 10.1136/bmj.m1985

54. Citu C, Gorun F, Motoc A, Ratiu A, Gorun OM, Burlea B, et al. Evaluation and comparison of the predictive value of 4C Mortality score, NEWS, and CURB-65 in poor outcomes in COVID-19 patients: a retrospective study from a single Center in Romania. *Diagnostics*. (2022) 12:703. doi: 10.3390/diagnostics12030703

55. Kostakis I, Smith GB, Prytherch D, Meredith P, Price C, Chauhan A, et al. The performance of the National Early Warning Score and National Early Warning Score 2 in hospitalised patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Resuscitation*. (2021) 159:150–7. doi: 10.1016/j.resuscitation.2020.10.039

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 09 October 2023
DOI 10.3389/fmed.2023.1229053

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Neeraj Srivastava,
University of California, United States
Meghan Bernier,
Johns Hopkins Medicine, United States

*CORRESPONDENCE
Jose E. Leon-Rojas
✉ jose.leon.rojas@udla.edu.ec

RECEIVED 25 May 2023
ACCEPTED 20 September 2023
PUBLISHED 09 October 2023

CITATION
Pinto-Villalba RS and Leon-Rojas JE (2023) Reported adverse events during out-of-hospital mechanical ventilation and ventilatory support in emergency medical services and critical care transport crews: a systematic review.
Front. Med. 10:1229053.
doi: 10.3389/fmed.2023.1229053

Reported adverse events during out-of-hospital mechanical ventilation and ventilatory support in emergency medical services and critical care transport crews: a systematic review

Ricardo Sabastian Pinto-Villalba[1,2,3] and Jose E. Leon-Rojas[4]*

[1]Carrera de Atención Prehospitalaria y en Emergencias, Universidad Central del Ecuador, Quito, Ecuador, [2]Facultad de Medicina, Carrera de Atención Prehospitalaria y en Emergencias, Universidad UTE, Quito, Ecuador, [3]Medignosis, Medical Research Department, Quito, Ecuador, [4]Escuela de Medicina, Universidad de las Américas (UDLA), Quito, Ecuador

Background: Emergency medical services (EMS) and critical care transport crews constantly face critically-ill patients who need ventilatory support in scenarios where correct interventions can be the difference between life and death; furthermore, challenges like limited staff working on the patient and restricted spaces are often present. Due to these, mechanical ventilation (MV) can be a support by liberating staff from managing the airway and allowing them to focus on other areas; however, these patients face many complications that personnel must be aware of.

Aims: To establish the main complications related to out-of-hospital MV and ventilatory support through a systematic review.

Methodology: PubMed, BVS and Scopus were searched from inception to July 2021, following the PRISMA guidelines; search strategy and protocol were registered in PROSPERO. Two authors carried out an independent analysis of the articles; any disagreement was solved by mutual consensus, and data was extracted on a pre-determined spreadsheet. Only original articles were included, and risk of bias was assessed with quality assessment tools from the National Institutes of Health.

Results: The literature search yielded a total of 2,260 articles, of which 26 were included in the systematic review, with a total of 9,418 patients with out-of-hospital MV; 56.1% were male, and the age ranged from 18 to 82 years. In general terms of aetiology, 12.2% of ventilatory problems were traumatic in origin, and 64.8% were non-traumatic, with slight changes between out-of-hospital settings. Mechanical ventilation was performed 49.2% of the time in prehospital settings and 50.8% of the time in interfacility transport settings (IFTS). Invasive mechanical ventilation was used 98.8% of the time in IFTS while non-invasive ventilation was used 96.7% of the time in prehospital settings. Reporting of adverse events occurred in 9.1% of cases, of which 94.4% were critical events, mainly pneumothorax in 33.1% of cases and hypotension in 27.6% of cases, with important considerations between type of out-of-hospital setting and ventilatory mode; total mortality was 8.4%.

Conclusion: Reported adverse events of out-of-hospital mechanical ventilation vary between settings and ventilatory modes; this knowledge could aid EMS providers in promptly recognizing and resolving such clinical situations, depending on the type of scenario being faced.

KEYWORDS

mechanical ventilation, EMS, critical care transport, complications, adverse event

Introduction

Emergency medical services and critical care transport crews are constantly facing critical patients who need ventilatory support for acute respiratory failure (ARF), airway protection in traumatic injuries, and high levels of sedation (1–3). The survival rate and favourable outcomes depend on the capacity to maintain physiologic end-tidal carbon dioxide (ETCO2) and oxygen levels and appropriate tidal volumes (1, 4, 5). The current methods used to achieve those goals in a prehospital setting include a bag-valve-mask device (BVM) and mechanical ventilation (MV).

Manual ventilation with a BVM is typically used for its dynamic and inexpensive applications; its use also requires less training when compared to MV – which can be complex and expensive (1). However, in an out-of-hospital setting (prehospital and interfacility), where limited staff, space, and equipment are common, MV can become a great ally, freeing the provider to attend to other urgent necessities (4). BVM and MV were considered equivalent for many years (6), but the reality is different; manual ventilation can maintain a physiologic ETCO2 only 16.7% of the time and provides inappropriate vital volumes – sometimes resulting in barotrauma (1, 7).

Mechanical ventilation through the means of either an instrument inside the trachea, named invasive mechanical ventilation (IMV), or without endotracheal devices, named non-invasive mechanical ventilation (NIMV), has demonstrated effective outcomes (8, 9). NIMV is useful in conscious patients who can maintain airway patency and is indicated mainly for chronic obstructive pulmonary disease (COPD), asthma exacerbations, and acute pulmonary oedema; it works by providing positive inspiratory pressure and maintaining end-expiratory pressure (PEEP), resulting in reduced inspiratory muscle work and fatigue (10). The main modalities used are continuous positive airway pressure (CPAP) or bilevel inspiratory positive airway pressure (BiPAP), which have shown reduced mortality and intubation rates in acute respiratory failure (11).

IMV is indicated when NIMV and other therapies have failed or when advanced airway management is needed to maintain patency and support severe injuries or illnesses (i.e., when controlled pulmonary pressures and specific parameters are needed) (1, 10). In contrast with NIMV, exact target parameters can be met by controlling pressure and/or volume and by using available pre-programmed modes (10). However, management of a mechanical ventilator requires specialized training and has a steep learning curve due to the high morbidity and mortality that ensue if the ventilatory settings are incorrect or monitoring is not done properly (1, 12). Patients can be exposed to iatrogenic ventilator-induced lung injury and disturbances in blood gases (i.e., hypocapnia, hypercapnia, hypoxia, and hyperoxia), especially when the aforementioned training is not done properly (10, 12).

Knowledge of these complications as well as the ventilatory modes used in an out-of-hospital setting can be helpful for EMS and critical care transport crews; such information can enable them to reduce mortality, identify the main ventilatory settings used in the field for mechanical ventilation, and anticipate the main adverse events that can arise during the procedure, reducing morbidity.

Methods

Protocol and registration

This study was made following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The research protocol as well as the full search criteria were uploaded and registered in PROSPERO (CRD42021279433).

Eligibility criteria

The language of the included studies was limited to English and Spanish. The eligibility criteria used can be found in Table 1.

All available studies, from the inception of the databases to July 28, 2021 were included.

Information sources

Studies were identified in PubMed, Scopus, and Biblioteca Virtual en Salud (BVS); the references of selected articles were also screened, and only one additional reference was extracted (13). No filters were used. BVS includes scientific literature from Latin America and the Caribbean, mainly written in Spanish; inclusion of such studies is limited in most systematic reviews that only consider the English language and therefore neglect literature from the Latin-American region, where traumatic events are highly prevalent.

Abbreviations: ARF, acute respiratory failure; BiPAP, bilevel inspiratory positive airway pressure; BVM, Bag-Valve-Mask-Device; BVS, Biblioteca Virtual en Salud; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ETCO2, end-tidal carbon dioxide; IFTS, interfacility transport settings; IMV, invasive mechanical ventilation; MV, mechanical ventilation; NIH, National Institutes of Health; NIMV, non-invasive mechanical ventilation; PEEP, end-expiratory pressure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 1 Summary of inclusion and exclusion criteria using the PICO framework.

	Inclusion	Exclusion
Patient		
	Adult human population (≥18 years old) Any ventilatory problem	Pediatric population (age <18 years old) Animal or manikins
Intervention		
	Out-of-hospital mechanical ventilation (prehospital or interfacility transfer) Any ventilatory mode	In-hospital mechanical ventilation Valve type ventilators like Boussignac or Vortran devices ECMO use
Comparison		
	Not applicable	Not applicable
Outcome		
	Mortality (in-hospital mortality, out-of-hospital mortality) Safety and associated problems during mechanical ventilation	
Study Design		
	Original studies	Literature reviews studies with less than 10 participants letters to the editor animal or biomechanical studies

Search

A search protocol was established, which can be found in the aforementioned PROSPERO registration. Search terms were tailored based on the PICO framework and the eligibility criteria; the following key terms, with variations, were used: mechanical ventilation, ventilation, out-of-hospital, mortality, safety, and adverse events.

Study selection

Two blinded reviewers conducted an independent and uniform evaluation of the chosen studies. Deduplication was performed automatically using Mendeley Reference Manager and two stages of screening were performed. The first stage involved the screening of titles and abstracts, while the second stage involved full-text review; after these, the data of the selected studies was extracted in a spreadsheet. Any discrepancies between the reviewers were resolved by discussion and mutual consensus.

Data items and collection process

For data extraction, we developed a spreadsheet with the following information: author, type of study, year of publication, number of ventilated patients, sex, age, type of out-of-hospital scenario (prehospital or interhospital as well as air or ground transport), ventilatory problem (traumatic, non-traumatic, and unclassified when the information provided in the study was not sufficient to classify the ventilatory problem), origin of the ventilatory problem (pulmonary, COVID-19, cardiovascular, neurologic, obstetric, septic, and other; unclassified was used when the author did not describe the origin of the problem), type of ventilation (invasive or non-invasive), mechanical ventilation mode (volume control, pressure control, pressure support, continuous airway pressure, CPAP+PS/BiPAP, and others), adverse events (divided in critical and non-critical), and mortality (divided in transport mortality and hospital mortality). If data was missing or inconsistent, we attempted to contact the authors; if they did not answer after repeated attempts, we considered it lost data. To note, due to the different illnesses of patients between out-of-hospital settings (prehospital and interfacility transport) and types of ventilation required (invasive or non-invasive) we decided to analyse them as different populations.

Risk of bias in individual studies

Both reviewers assessed the risk of bias independently using the Study Quality Assessment Tools from the National Institutes of Health (NIH). Studies were graded as either minimally low, moderately low, or high risk of bias. If answering yes in less than 50% of the questions, the study was graded as poor and hence had a high risk of bias; if between 50 and 79%, it was graded as fair and hence had a moderately low risk of bias; and if 80% or more, it was graded as good and hence had a minimally low risk of bias, as done in a previous review (14).

Results

The searches from the inception of the databases to July 28, 2021 yielded a total of 2,260 results. Following the removal of duplicate entries, a subset of 1,399 articles remained for further evaluation during the screening phase. The complete process of article screening can be found in Figure 1.

A total of 26 studies were finally included (3, 6, 9, 15-37); these studies, with their year of publication, design, and bias assessment, are shown in Table 2.

A total of 9,418 patients who received out-of-hospital mechanical ventilation were included in our research. Among these individuals, 56.1% were identified as male. The age range of all participants spanned from 18 to 82 years. In the context of the out-of-hospital setting, 49.2% of patients received MV in a prehospital setting, while the remaining received it in an IFTS. In the prehospital setting, the prevailing ventilatory mode was found to be CPAP (NIMV), administered to a total of 2,911 patients. In contrast, volume control (IMV) was administered to 1,702 patients in the IFTS. A general summary of all ventilated patients can be found in Table 3.

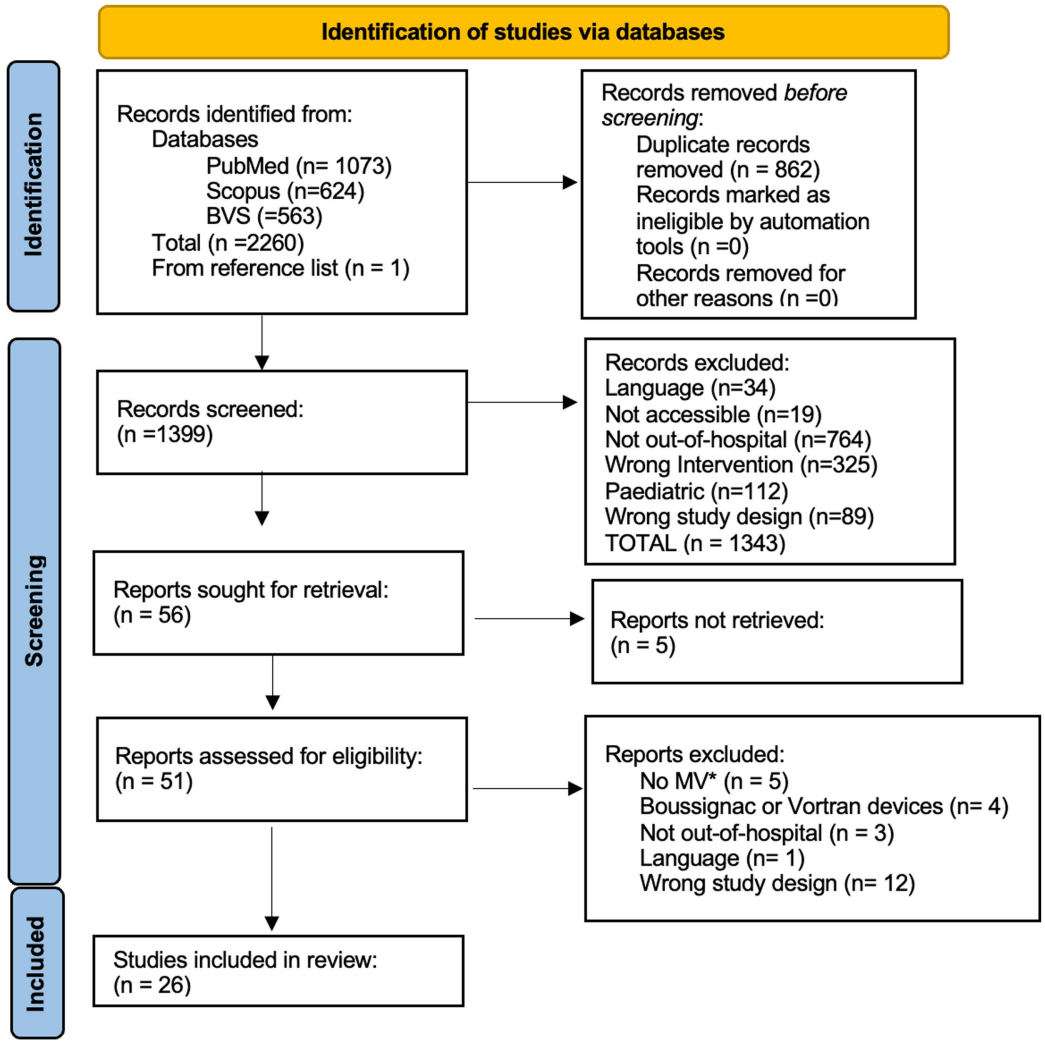


FIGURE 1
PRISMA flow chart.

Mechanical ventilation in the prehospital setting

In prehospital settings, a total of 4,631 patients underwent mechanical ventilation. Among these patients, 49% were identified as female. Notably, NIMV was the primary method of ventilatory support in 96.7% of the instances, while just 3.3% of the cases used IMV. We further subclassified these based on the ventilatory mode used (Figure 2).

The analysis of the data indicates that non-traumatic ventilatory causes are more prevalent than traumatic ventilatory causes in the prehospital setting, accounting for 94.6 and 5.4%, respectively. Please see Figure 3 for the subclassification of non-traumatic aetiologies.

Adverse events that were seen during ventilation in the prehospital setting were documented in 1.8% of patients. These events were categorized based on their potential to cause life-threatening situations, with critical events accounting for 16% and non-critical events accounting for 84% of the reported cases. It is worth noting that adverse events were only recorded in relation to NIMV, as shown in Figure 4. The most critical events seen in this study were hypotension, which occurred in 50% of cases, and pneumothorax, which occurred in 37.5% of cases. These events were predominantly observed in patients with non-traumatic injuries, namely those with cardiovascular or pulmonary illnesses.

The vast majority of pre-hospital transfers, accounting for 99.6% of cases, were conducted by ground transportation. Among these cases, 661 patients, or 14.2% of the total, were reported to have died upon admission. Notably, no fatalities were recorded during the actual transport phase in the dataset under analysis.

Mechanical ventilation in the interfacility transport setting

In the IFTS, a total of 4,787 individuals underwent mechanical ventilation. Among these, 68% were male and the majority (98.8%)

TABLE 2 Risk of bias assessment.

	Study	Year	Study design	Risk of bias
1	Barillo et al. (15)	1997	Cross-sectional	High Risk
2	Cheskes et al. (36)	2013	Case-control	Moderately Low Risk
3	Craven et al. (17)	2000	Randomized controlled trial	Moderately Low Risk
4	El Sayed (9)	2019	Case-control	Moderately Low Risk
5	Fuller et al. (27)	2020	Pilot randomized controlled trial	Low Risk
6	Gardtman et al. (18)	2000	Cross-sectional	Moderately Low Risk
7	Garrote et al. (20)	2015	Case-control	Moderately Low Risk
8	Gartner et al. (21)	2020	Case-control	Moderately Low Risk
9	Garuti et al. (22)	2010	Case-control	Moderately Low Risk
10	Hubble et al. (23)	2006	No randomized controlled trial	Moderately Low Risk
11	Johannigman et al. (6)	1995	Cross-sectional	Moderately Low Risk
12	Jouffroy et al. (30)	2019	Cohort Study	Moderately Low Risk
13	Jouffroy et al. (24)	2019	Cohort Study	Moderately Low Risk
14	Kallio et al. (35)	2003	Cohort Study	Moderately Low Risk
15	Kashyap et al. (26)	2016	Cohort Study	Moderately Low Risk
16	Kosowsky et al. (19)	2001	Case series	Low Risk
17	Le Cong and Robertson (28)	2013	Cross-sectional	Moderately Low Risk
18	Maddry et al. (3)	2018	Cohort Study	Moderately Low Risk
19	Michelet et al. (29)	2017	Cross-sectional	Moderately Low Risk
20	Painvin et al. (31)	2021	Cohort Study	Moderately Low Risk
21	Plaisance et al. (32)	2007	Randomized controlled trial	Low Risk
22	Roessler et al. (33)	2012	Pilot randomized controlled trial	Moderately Low Risk
23	Seethala et al. (34)	2020	Cross-sectional	Moderately Low Risk
24	Singh et al. (25)	2009	Cohort Study	Moderately Low Risk
25	Singh et al. (16)	2014	Cohort Study	Moderately Low Risk
26	Thompson et al. (37)	2008	Randomized controlled trial	Moderately Low Risk

got IMV as their primary form of ventilatory support, while a smaller proportion (1.2%) used NIMV. We further subclassified these based on the ventilatory mode used (Figure 5).

Similar to the prehospital setting, non-traumatic causes of ventilatory issues were more often seen than traumatic causes, with a prevalence of 36.1% compared to 20.8%. Please refer to Figure 6 for a breakdown of the subcategories of non-traumatic causes. Unfortunately, in this group, there was an important lack of data that prevented us from classifying the aetiology of the ventilatory problems (43.1% had to be categorized as unclassified).

Reported adverse events during ventilation in the IFTS occurred in 16.9% of patients. Among these occurrences, 99.3% were classified as critical, while the remaining 0.7% were considered non-critical. The majority of adverse events were recorded in patients receiving IMV, accounting for 97.5% of cases, while only 2.5% of cases were associated with NIMV. Each of these categories was further divided into specific types of events and presented in Figure 7. The two main critical events reported in this group of patients were pneumothorax (33%), mainly in traumatic illnesses (i.e., blast or penetrating injuries), and hypotension (27.4%), mainly in non-traumatic injuries (i.e., cardiovascular or pulmonary illness). It is noteworthy that despite the relatively high occurrence of these events, overall mortality remained relatively low at 3%.

The majority of interfacility transports, around 82%, were conducted via land transportation, while the remaining proportion used air transport. Among the whole population of mechanically ventilated patients in the IFTS, a mortality rate of 3% was observed upon arrival. No instances of death were recorded during the transit phase in the data that was analysed.

Discussion

This systematic review was performed to assess the use of out-of-hospital mechanical ventilation, its features, reported adverse events, and mortality.

The attention of critically-ill patients in out-of-hospital settings is a challenge for EMS and critical care transport crews that need to expertly handle multiple complex procedures and therapies in a limited physical space with minimal equipment and staff – often following different protocols based on the institution or regulatory bodies of the country (16). The use of equipment in these instances, either at the location of

TABLE 3 General results of out-of-hospital mechanical ventilation.

Data Item	*n*=	%
Patients	9,418	100%
Male	4,015	56.1%
Female	3,148	43.9%
Range of age (years)	18–82	
Ventilatory problem		
Traumatic	1,153	12.2%
Non traumatic	6,111	64.9%
Unclassified	2,154	22.9%
Out-of-hospital environment		
Prehospital	4,631	49.2%
Interfacility Transport	4,787	50.8%
Type of transport		
Air	895	9.5%
Ground	8,523	90.5%
Ventilated patients		
Invasive mechanical ventilation	4,880	51.8%
Non-invasive mechanical ventilation	4,538	48.2%
Adverse events during mechanical ventilation	860	9.1%
Critical events	812	94.4%
Noncritical events	48	5.6%
Mortality	791	8.4%

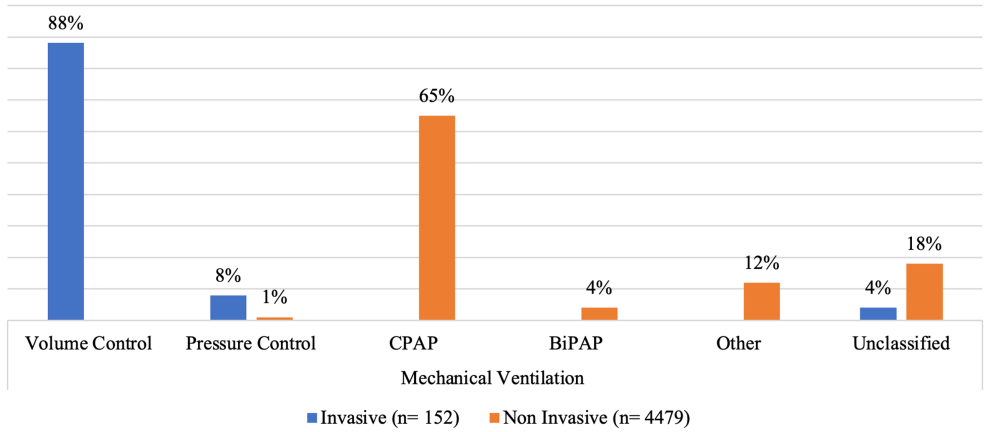


FIGURE 2
Prehospital setting: subclassification of mechanical ventilation modes.

attention or during transportation between centres, can help prolong life until definitive care in a hospital (16). In the course of these events, the EMS and critical care transport crews need to recognize all possible life-threatening conditions associated with the illness, as well as the adverse events that may arise from the use of devices, in order to prevent them from happening (16). However, it should be noted that our study does not establish a direct causal relationship between complications and mechanical ventilation, primarily due to limitations in the design and

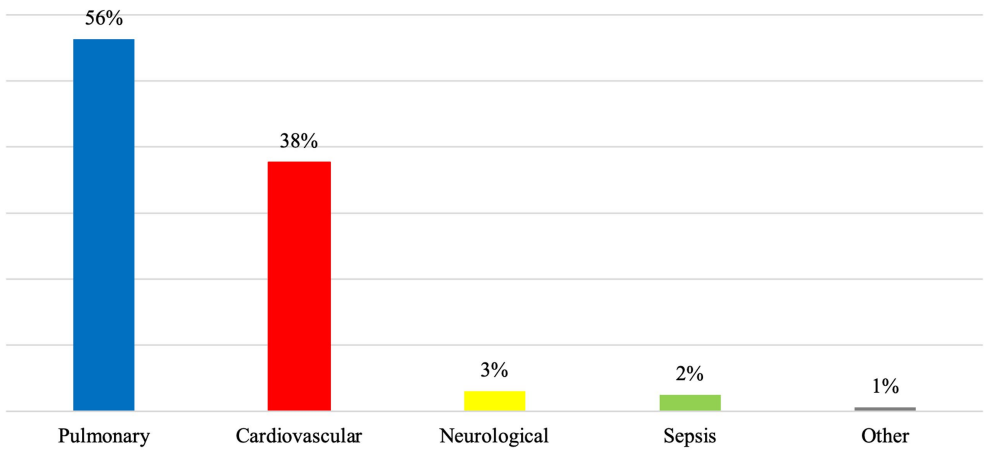


FIGURE 3
Prehospital setting: subclassification of non-traumatic aetiologies.

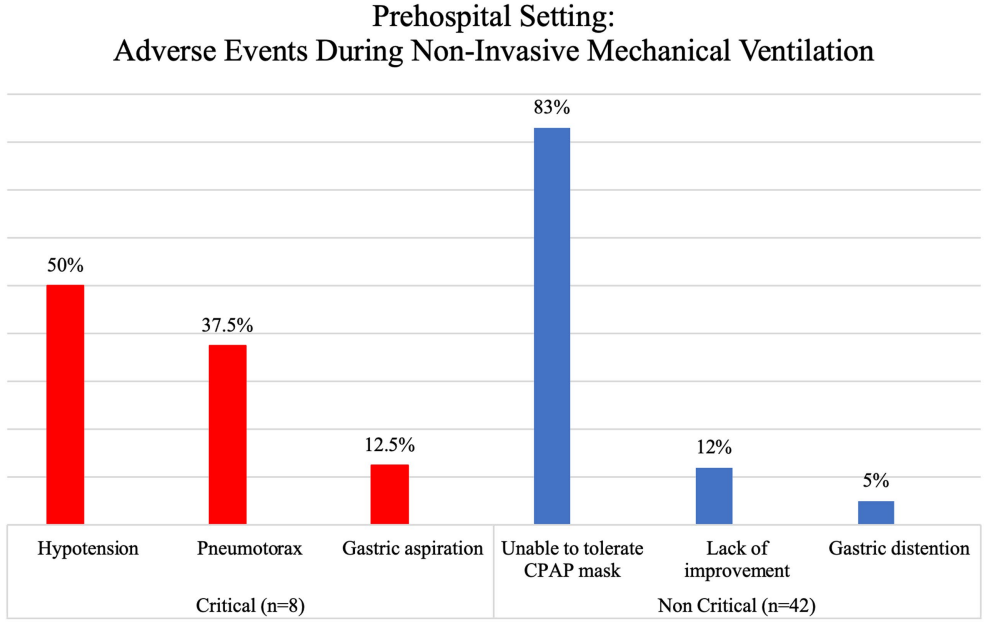


FIGURE 4
Prehospital setting: adverse events during mechanical ventilation.

available information in the studies included. Nonetheless, our study does emphasize the frequency of adverse events in patients receiving mechanical ventilation. It underscores the importance of considering these complications when managing patients with traumatic or non-traumatic conditions, providing an opportunity to proactively address them based on the specific patient characteristics, the mode of mechanical ventilation employed, or the type of out-of-hospital setting.

Mechanical ventilation was typically used in hospitals, but over time this procedure became increasingly common in the prehospital setting – during transports and primary attention (6, 10, 38). In our study, we found an ample range of ages (18–82), which might be due to the fact that this procedure is being used more frequently in young people due to traumatic conditions such as burns, brain lesions, and combat injuries (3, 15), while still being beneficial for older adults that usually have chronic conditions or emergent conditions elicited by previous illnesses like acute cardiogenic pulmonary oedema or exacerbations of chronic obstructive pulmonary disease (COPD) (18, 19).

Mechanical ventilation during interfacility transport is more common than in the prehospital setting, especially during ground

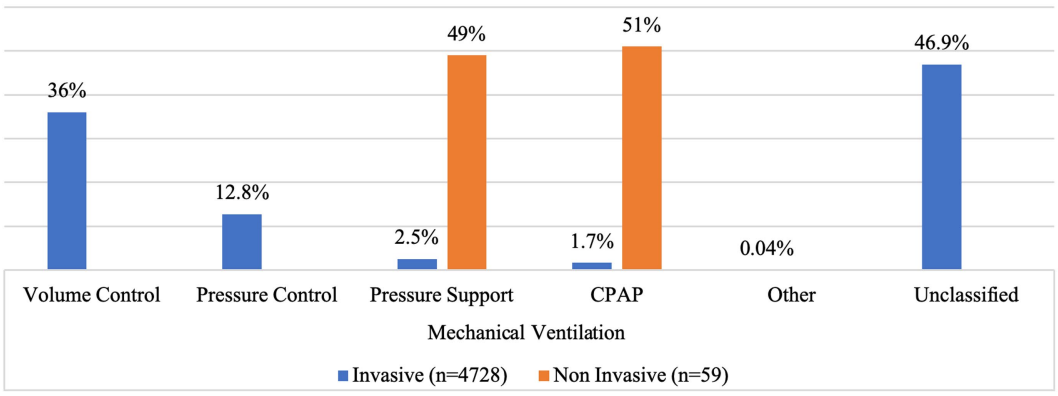


FIGURE 5
Interfacility transport setting: subclassification of mechanical ventilation modes.

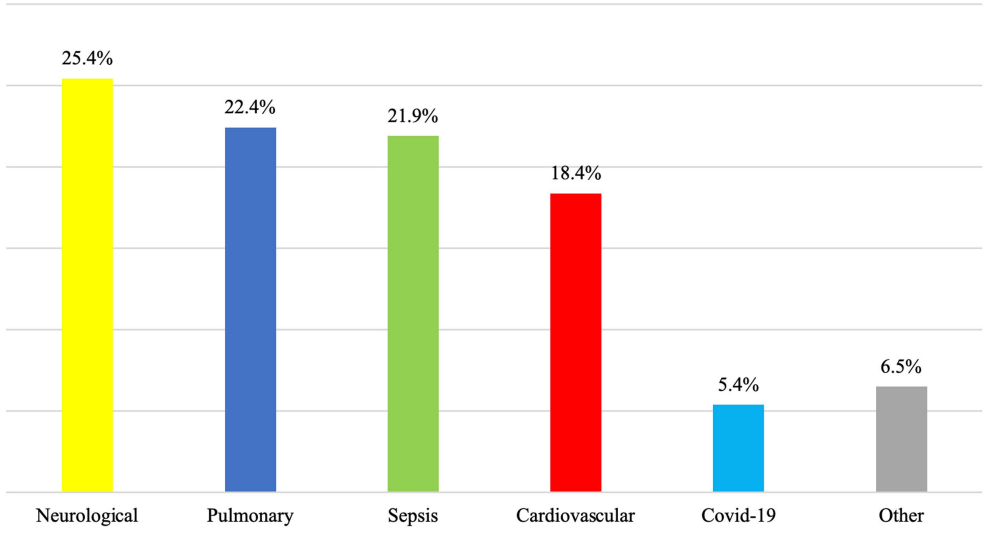


FIGURE 6
Interfacility transport setting: subclassification of non-traumatic aetiologies.

transport, which happens to be the most common modality due to higher availability and lower cost when compared to air ambulances (39); in our study, 90.5% were transported by ground using a variety of ventilatory modalities.

The means of mechanical ventilation were evenly distributed between invasive 51.8% (mainly in IFTS) and non-invasive 48.2% (mainly in prehospital settings). NIMV was represented primarily by CPAP (64.4%), which is not surprising given that previous studies have shown improvement on vital signs, reduction in short-term mortality, and less need for endotracheal intubation in patients with acute pulmonary oedema and chronic obstructive pulmonary disease (COPD) when using this ventilatory mode (40–42). In contrast, the main modality for IMV in out-of-hospital settings was volume control ventilation (37.6%), while the unclassified category represented 45.6% of all IMV patients. Showcasing that, studies assessing IMV in a prehospital setting often do not provide enough information to clearly determine the modality being used, leading to the loss of valuable information such as detecting common complications of each modality that might differ from those in a hospital setting. This is especially concerning when considering that the correct use of a ventilator with lung-protective parameters by properly trained prehospital

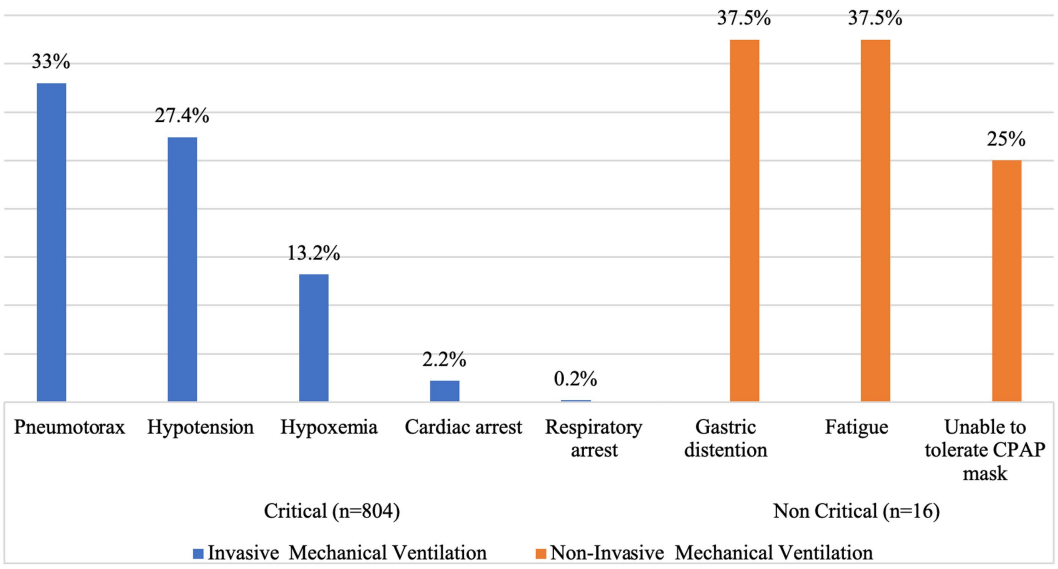


FIGURE 7
Interfacility transport setting: adverse events during mechanical ventilation.

professionals increases survival by improving the chances of accessing appropriate medical care (3, 24).

Adverse events

Hypotension and pneumothorax

Critically ill patients can face multiple adverse events during out-of-hospital care – evidence suggests an incidence of one in fifteen transports, with hypotension being a common complication in 4.4–11.9% of cases (16, 25, 43). This contrasts with our findings that show a higher incidence of pneumothorax than of hypotension (33% vs. 27.4%) in IFTS, possibly due to the underlying condition that required ventilation in the first place; however, in the pre-hospital setting, hypotension does show a higher incidence than pneumothorax (50% vs. 37.5%). However, we could not directly correlate hypotension or pneumothorax with the use of out-of-hospital mechanical ventilation due to the lack of complete data in the available evidence that would allow us to establish causality. Regardless of the aetiology, EMS and critical care transport personnel that use mechanical ventilation in out-of-hospital settings must be on high alert for such events and be prepared to solve them when they arise.

Oxygen levels

Hypoxia is a common condition in the prehospital setting, often requiring ventilatory support (44–46). Although this adverse event was less common than hypotension or pneumothorax in our analysis (13.1%), the EMS and critical care transport crews need to take it into account and monitor closely the oxygen availability and consumption along the transport; an ample supply of oxygen should be available in the vehicle, especially when expecting to travel long distances.

Although hypoxia is frequently discussed in the literature, hyperoxia – which can go unnoticed – is equally harmful to the patient; hence, prehospital responders must target SpO_2 values above 94% and below 96% (30, 47).

Mortality

Although our reported mortality is relatively low – 8.4% overall for out-of-hospital mortality, 3% for the IFTS, and 14.3% for the prehospital setting – it correlates with epidemiological prehospital mortality studies in airlifted and ground patients (8.2 and 14.6%, respectively) (48). Continuing education and appropriate training of responders might help in improving the safety of this procedure. We performed a sub-analysis that revealed that most of the mortality occurred in airlifted patients; however, this is more likely explained by the severity of illness (requiring faster transport through the air) than by the direct effect of the type of transport or the use of mechanical ventilation. Therefore, we encourage out-of-hospital personnel to train in the proper use of all of their available devices, including the mechanical ventilator, in order to provide the best treatment possible until definitive care can be obtained.

Limitations

Our analysis was dependent on the quality of the data in the included studies, some of which lacked specific information that prevented an in-depth analysis of correlations or causality between mechanical ventilation and patient complications due to high heterogeneity. Regardless of comparators, when all patients who received the intervention are considered, less than 10% suffered an adverse event or manifestation of the underlying pathology associated with the condition that led to the intervention. Most of the studies

analysed transported patients as a whole (i.e., including ventilated and non-ventilated), which precluded a subgroup exploration of aetiology, diagnosis, and complications or number of complications per patient of only those being mechanically ventilated; almost 22% of the patients included in this review had to be categorized as "unclassified" due to missing information. Additionally, there was little information regarding the ventilatory modes used and ventilatory settings, especially with IMV, which prevented us from properly assessing if the ventilatory modality was related to mortality or morbidity.

Conclusion

The mechanical ventilator can be a helpful device in an out-of-hospital setting given that it liberates EMS and critical care transport personnel to provide support for the patient's condition during the transport in different areas other than ventilation. Additionally, achieving proper ventilatory parameters – while avoiding hypoxemia, low or high tidal volumes, and hypo or hypercapnia – becomes easier and significantly superior to using the BVM device.

Adverse events in out-of-hospital mechanical ventilation vary depending on the type of out-of-hospital setting and ventilatory mode. Although adverse events around mechanical ventilation are limited, the EMS and critical care transport crews must be trained and prepared to promptly recognize them or identify conditions that can lead to them; training and continuing education are paramount to achieving this.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

RP-V: conceptualization, data curation, formal analysis, investigation, visualization, writing – original draft preparation, and writing – review & editing. JL-R: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, and writing – review & editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the (Dirección General de Investigación y Vinculación, Universidad de Las Américas, Quito, Ecuador).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. McLachlan B, Bilbrey C, Mausner K, Lenz TJ. Effectiveness of manual ventilation in intubated helicopter emergency services-transported trauma patients. *Air Med J*. (2019) 38:273–5. doi: 10.1016/j.amj.2019.03.013

2. Williams TA, Finn J, Perkins GD, Jacobs IG. Prehospital continuous positive airway pressure for acute respiratory failure: a systematic review and meta-analysis. *Prehosp Emerg Care*. (2013) 17:261–73. doi: 10.3109/10903127.2012.749967

3. Maddry JK, Mora AG, Savell SC, Perez CA, Mason PE, Aden JK, et al. Impact of critical care air transport team (CCATT) ventilator management on combat mortality. *J Trauma Acute Care Surg*. (2018) 84:157–64. doi: 10.1097/TA.0000000000001607

4. Weiss SJ, Ernst AA, Jones R, Ong M, Filbrun T, Augustin C, et al. Automatic transport ventilator versus bag valve in the EMS setting: a prospective, randomized trial. *South Med J*. (2005) 98:970–6. doi: 10.1097/01.smj.0000182177.01436.70

5. COMACARE study groupJakkula P, Reinikainen M, Hästbacka J, Pettilä V, Loisa P, et al. Targeting low- or high-normal carbon dioxide, oxygen, and mean arterial pressure after cardiac arrest and REsuscitation: study protocol for a randomized pilot trial. *Trials*. (2017) 18:507. doi: 10.1186/s13063-017-2257-0

6. Johannigman JA, Branson RD, Johnson DJ, Davis K, Hurst JM. Out-of-hospital ventilation: bag-valve device vs transport ventilator. *Acad Emerg Med*. (1995) 2:719–24. doi: 10.1111/j.1553-2712.1995.tb03624.x

7. Siegler J, Kroll M, Wojcik S, Moy HP. Can EMS providers provide appropriate tidal volumes in a simulated adult-sized patient with a pediatric-sized bag-valve-mask? *Prehosp Emerg Care*. (2017) 21:74–8. doi: 10.1080/10903127.2016.1227003

8. Pandor A, Thokala P, Goodacre S, Poku E, Stevens JW, Ren S, et al. Pre-hospital non-invasive ventilation for acute respiratory failure: a systematic review and cost-effectiveness evaluation. *Health Technol Assess*. (2015) 19:1–102. doi: 10.3310/hta19420

9. El Sayed MJ, Tamim H, Mailhac A, Mann NC. Impact of prehospital mechanical ventilation: a retrospective matched cohort study of 911 calls in the United States. *Medicine*. (2019) 98:e13990. doi: 10.1097/MD.0000000000013990

10. Rose L. Management of critically ill patients receiving noninvasive and invasive mechanical ventilation in the emergency department. *Open Access Emerg Med*. (2012) 4:5–15. doi: 10.2147/OAEM.S25048

11. Goodacre S, Stevens JW, Pandor A, Poku E, Ren S, Cantrell A, et al. Prehospital noninvasive ventilation for acute respiratory failure: systematic review, network meta-analysis, and individual patient data meta-analysis. *Acad Emerg Med*. (2014) 21:960–70. doi: 10.1111/acem.12466

12. Stephens RJ, Siegler JE, Fuller BM. Mechanical ventilation in the prehospital and emergency department environment. *Respir Care*. (2019) 64:595–603. doi: 10.4187/respcare.06888

13. Sahu AK, Timilsina G, Mathew R, Jamshed N, Aggarw P. "Six-dial strategy"-mechanical ventilation during cardiopulmonary resuscitation. *Indian J Crit Care Med*. (2020) 24:487–9. doi: 10.5005/jp-journals-10071-23464

14. Ghaffari-Rafi A, Peterson C, Leon-Rojas JE, Tadokoro N, Lange SF, Kaushal M, et al. The role of magnetic resonance imaging to inform clinical decision-making in acute spinal cord injury: a systematic review and meta-analysis. *J Clin Med*. (2021) 10:4948. doi: 10.3390/jcm10214948

15. Barillo DJ, Dickerson EE, Cioffi WG, Mozingo DW, Pruitt BA. Pressure-controlled ventilation for the long-range aeromedical transport of patients with burns. *J Burn Care Rehabil*. (1997) 18:200–5. doi: 10.1097/00004630-199705000-00004

16. Singh JM, MacDonald RD, Ahghari M. Critical events during land-based interfacility transport. *Ann Emerg Med*. (2014) 64:9–15. doi: 10.1016/j.annemergmed.2013.12.009

17. Craven RA, Singletary N, Bosken L, Sewell E, Payne M, Lipsey R. Use of bilevel positive airway pressure in out-of-hospital patients. *Acad Emerg Med*. (2000) 7:1065–8.

18. Gardtman M, Waagstein L, Karlsson T, Herlitz J. Has an intensified treatment in the ambulance of patients with acute severe left heart failure improved the outcome? *Eur J Emerg Med.* (2000) 7:15–24.

19. Kosowsky JM, Stephanides SL, Branson RD, Sayre MR. Prehospital use of continuous positive airway pressure (CPAP) for presumed pulmonary edema: a preliminary case series. *Prehosp Emerg Care.* (2001) 5:190–6.

20. Garrote JI, Aylagas D, Gutierrez JM, Sinisterra JA, Gowran BM, Medina A, et al. Noninvasive Mechanical Ventilation in Helicopter Emergency Medical Services Saves Time and Oxygen and Improves Patient and Mission Safety: A Pilot Study. *Air Med J.* (2015) 34:218–22.

21. Gartner BA, Fehlmann C, Suppan L, Niquille M, Rutschmann OT, Sarasin F. Effect of noninvasive ventilation on intubation risk in prehospital patients with acute cardiogenic pulmonary edema: a retrospective study. *Eur J Emerg Med.* (2020) 27:54–8.

22. Garuti G, Bandiera G, Cattaruzza MS, Gelati L, Osborn JF, Toscani S, et al. Out-of-hospital helmet CPAP in acute respiratory failure reduces mortality: a study led by nurses. *Monaldi Arch Chest Dis.* (2010) 73:145–51.

23. Hubble MW, Richards ME, Jarvis R, Millikan T, Young D. Effectiveness of prehospital continuous positive airway pressure in the management of acute pulmonary edema. *Prehosp Emerg Care.* (2006) 10:430–9.

24. Jouffroy R, Saade A, Pegat-Toquet A, Philippe P, Carli P, Vivien B. Pre-hospital mechanical ventilation in septic shock patients. *Am J Emerg Med.* (2019) 37:1860–3. doi: 10.1016/j.ajem.2018.12.047

25. Singh JM, Ferguson ND, MacDonald RD, Stewart TE, Schull MJ. Ventilation practices and critical events during transport of ventilated patients outside of hospital. *Prehospital Emerg Care.* (2009) 13:316–23. doi: 10.1080/10903120902935264

26. Kashyap R, Anderson PW, Vakil A, Russi CS, Cartin-Ceba R. A retrospective comparison of helicopter transport versus ground transport in patients with severe sepsis and septic shock. Int. *J Emerg Med.* (2016) 9.

27. Fuller G, Keating S, Goodacre S, Herbert E, Perkins G, Rosser A, et al. Is a definitive trial of prehospital continuous positive airway pressure versus standard oxygen therapy for acute respiratory failure indicated? The ACUTE pilot randomised controlled trial. *BMJ Open.* (2020) 10:e035915.

28. Le Cong M, Robertson A. A 3-year retrospective audit of the use of noninvasive positive pressure ventilation via the Oxylog 3000 transport ventilator during air medical retrievals. *Air Med J.* (2013) 32:126–8.

29. Michelet P, Bouzana F, Charmensat O, Tiger F, Durand-Gasselin J, Hraiech S, et al. Acute respiratory failure after drowning: A retrospective multicenter survey. *Eur J Emerg Med.* (2017) 24:295–300.

30. Jouffroy R, Saade A, Saint Martin LC, Philippe P, Carli P, Vivien B. Prognosis value of partial arterial oxygen pressure in patients with septic shock subjected to pre-hospital invasive ventilation. *Am J Emerg Med.* (2019) 37:56–60. doi: 10.1016/j.ajem.2018.04.050

31. Painvin B, Messet H, Rodriguez M, Lebouvier T, Chatellier D, Soulat L, et al. Inter-hospital transport of critically ill patients to manage the intensive care unit surge during the COVID-19 pandemic in France. *Ann Intensive Care.* (2021):11.

32. Plaisance P, Pirracchio R, Berton C, Vicaut E, Payen D. A randomized study of out-of-hospital continuous positive airway pressure for acute cardiogenic pulmonary oedema: physiological and clinical effects. *Eur Heart J.* (2007) 28:2895–901.

33. Roessler MS, Schmid DS, Michels P, Schmid O, Jung K, Stöber J, et al. Early out-of-hospital non-invasive ventilation is superior to standard medical treatment in patients with acute respiratory failure: A pilot study. *Emer Med J.* (2012) 29:409–14.

34. Seethala RR, Frakes MA, Cocchi MN, Cohen JE, Dargin J, Friedman F, et al. Feasibility and Safety of Prone Position Transport for Severe Hypoxemic Respiratory Failure Due to Coronavirus Disease 2019. *Crit Care Explor.* (2020) 2:e0293.

35. Kallio T, Kuisma M, Alaspää A, Rosenberg PH. The use of prehospital continuous positive airway pressure treatment in presumed acute severe pulmonary edema. *Prehosp Emerg Care.* (2003) 7:209–13.

36. Cheskes S, Turner L, Thomson S, Aljerian N. The impact of prehospital continuous positive airway pressure on the rate of intubation and mortality from acute out-of-hospital respiratory emergencies. *Prehosp Emerg Care.* (2013) 17:435–41.

37. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ. Out-of-hospital continuous positive airway pressure ventilation versus usual care in acute respiratory failure: a randomized controlled trial. *Ann Emerg Med.* (2008) 52:241.e1.

38. Girotti MJ, Pagliarello G, Todd TR, Demajo W, Cain J, Walker P, et al. Physician-accompanied transport of surgical intensive care patients. *Can J Anaesth.* (1988) 35:303–8. doi: 10.1007/BF03010636

39. Taylor CB, Stevenson M, Jan S, Middleton PM, Fitzharris M, Myburgh JA. A systematic review of the costs and benefits of helicopter emergency medical services. *Injury.* (2010) 41:10–20. doi: 10.1016/j.injury.2009.09.030

40. Simpson PM, Bendall JC. Prehospital non-invasive ventilation for acute cardiogenic pulmonary oedema: an evidence-based review. *Emerg Med J.* (2011) 28:609–12. doi: 10.1136/emj.2010.092296

41. Masip J. Noninvasive ventilation in acute heart failure. *Curr Heart Fail Rep.* (2019) 16:89–97. doi: 10.1007/s11897-019-00429-y

42. Williams B, Boyle M, Robertson N, Giddings C. When pressure is positive: a literature review of the prehospital use of continuous positive airway pressure. *Prehosp Disaster Med.* (2013) 28:52–60. doi: 10.1017/S1049023X12001562

43. Nawrocki PS, Poremba M, Lawner BJ. Push dose epinephrine use in the management of hypotension during critical care transport. *Prehospital Emerg Care.* (2020) 24:188–95. doi: 10.1080/10903127.2019.1588443

44. L'Her E, Duquesne F, Paris A, Mouline J, Renault A, Garo B, et al. Spontaneous positive end-expiratory pressure ventilation in elderly patients with cardiogenic pulmonary edema. Assessment in an emergency admissions unit. *Presse Med.* (1998) 27:1089–94.

45. Britos M, Smoot E, Liu KD, Thompson BT, Checkley W, Brower RG. The value of positive end-expiratory pressure and Fio2 criteria in the definition of the acute respiratory distress syndrome. *Crit Care Med.* (2011) 39:2025–30. doi: 10.1097/CCM.0b013e31821cb774

46. Roessler M. Non-invasive ventilation in prehospital emergency medicine. *Anasthesiol Intensivmed Notfallmed Schmerzther.* (2008) 43:264–6. doi: 10.1055/s-2008-1076608

47. Cumpstey AF, Oldman AH, Martin DS, Smith A, Grocott MPW. Oxygen targets during mechanical ventilation in the ICU: a systematic review and meta-analysis. *Crit Care Explor.* (2022) 4:e0652. doi: 10.1097/CCE.0000000000000652

48. Alstrup K, Petersen JAK, Sollid S, Johnsen SP, Rognås L. Mortality and hospitalisation in the Danish helicopter emergency medical service (HEMS) population from 2014 to 2018: a national population-based study of HEMS triage. *BMJ Open. 1228* (2020) 10:e038718. doi: 10.1136/bmjopen-2020-038718

frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 19 October 2023
DOI 10.3389/fmed.2023.1264928

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Jose Eduardo Leon-Rojas,
University of the Americas, Ecuador
Andrea Glotta,
Istituto Cardiocentro Ticino, Switzerland

*CORRESPONDENCE
Jia Huang
✉ hjsunnyvale@hotmail.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 21 July 2023
ACCEPTED 26 September 2023
PUBLISHED 19 October 2023

CITATION
Wu Q, Cen F, Wang G and Huang J (2023) Early application of awake extracorporeal membrane oxygenation in pneumocystis jirovecii pneumonia complicated with severe acute respiratory distress syndrome: a case report. *Front. Med.* 10:1264928.
doi: 10.3389/fmed.2023.1264928

Early application of awake extracorporeal membrane oxygenation in pneumocystis jirovecii pneumonia complicated with severe acute respiratory distress syndrome: a case report

Qinglin Wu†, Fulan Cen†, Guowei Wang and Jia Huang*

Department of Intensive Care Unit, Shenzhen Third People's Hospital, Shenzhen, China

Introduction: Patients suffering from severe acute respiratory distress syndrome (ARDS) are usually treated with mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) has traditionally been considered a life-saving therapy and was reserved as a last resort when other treatment options were exhausted. However, this report outlines our successful initial experience with early implementation of awake venovenous extracorporeal membrane oxygenation (VV-ECMO) in a case of pneumocystis jirovecii pneumonia complicated by severe acute respiratory distress syndrome (ARDS), offering a promising new approach for recovery.

Case presentation: We present a case report of the effective application of awake VV-ECMO in a 29 years-old man with severe ARDS caused by pneumocystis jirovecii pneumonia. The patient initially received antibiotic treatment and non-invasive ventilation (NIV) for respiratory distress, but these interventions failed to improve the worsening dyspnea that occurred in the patient. Following the combined antifungal therapy, high-flow nasal cannula (HFNC) oxygen therapy, and VV-ECMO for a duration of 7 days, the patient's symptoms improved, showing relief.

Conclusion: Awake VV-ECMO proved to be an effective treatment for critically ill patients with ARDS, avoiding the need for invasive mechanical ventilation. However, increased clinical evidence is needed to verify whether awake ECMO could be widely used in severe ARDS caused by other diseases or conditions.

KEYWORDS

extracorporeal membrane oxygenation (ECMO), venovenous ECMO (VV-ECMO), acute respiratory distress syndrome (ARDS), pneumocystis jirovecii pneumonia (PJP), case report

1. Introduction

Pneumocystis jirovecii pneumonia (PJP) is a significant concern in patients who have received solid organ or hematopoietic stem cell transplants. These patients often require immunosuppressive medications to prevent rejection of the transplanted organ or graft-versus-host disease, which can weaken their immune system and make them more susceptible to

opportunistic infections such as PJP (1). As a lung infection, PJP may result in respiratory failure, necessitating advanced respiratory support (2). Venovenous extracorporeal membrane oxygenation (VV-ECMO) has traditionally been employed as a salvage therapy to treat patients with respiratory failure under adequate sedation and analgesia (3, 4). In recent years, awake extracorporeal membrane oxygenation (ECMO) is often initiated earlier in the course of severe acute respiratory distress syndrome (ARDS) to avoid potential detrimental effects of mechanical ventilation, such as ventilator-induced lung injury (5). Awake ECMO, a novel therapeutic method allowing patients to remain conscious and breathe spontaneously without mechanical ventilation, is increasingly used due to its benefits such as lower incidence of ventilator-associated pneumonia, prevention of ventilator-induced diaphragm dysfunction, reduction of delirium, better rehabilitation, and treatment compliance (5, 6). However, early initiation of awake ECMO applied in a critical case of PJP with severe ARDS is exceedingly rare. Addressing this issue is urgent to improve the current status of severe ARDS cases, marked by stubbornly high mortality, prolonged length of stay (LOS), and increased hospitalization costs (7, 8). This report presents the successful early use of awake ECMO in PJP treatment, offering unique perspectives and insights for the management of these patients.

2. Case presentation

A 29 years-old man was hospitalized in May 2023, presenting with a 3 days history of fever and dyspnea. The patient had previously been diagnosed with primary biliary cirrhosis (PBC) 9 years ago and had been on a long-term use of ursodeoxycholic acid (UDCA). He denied any related family history. On 6 November 2021, the patient was admitted to the hepatology department presenting symptoms of jaundice and lower limb edema. After admission, the patient was diagnosed with acute-on-chronic liver failure (ACLF) and underwent liver transplantation surgery after 1 year. The patient adhered to the prescribed regimen of tacrolimus and mycophenolate mofetil after liver transplantation to prevent transplant rejection. The physical examination of the patient revealed a temperature of 38.4°C, a heart rate of 84 beats/min, a respiratory rate of 20 breaths/min, an oxygen saturation (SpO_2) of 99%, a blood pressure of 120/82 mmHg, and lung auscultation revealed diminished sounds with a few moist crackles heard. Other physical examinations were negative. Blood tests indicated a white blood cell count of 3.75×10^9/L, a neutrophilic granulocyte percentage (NE%) of 77.6%, a procalcitonin (PCT) of 21.8 ng/mL, and a C-reactive protein (CRP) of 22 mg/L. The results of 1-3-β-D-glucan and G-lipopolysaccharide tests were negative, and the absolute counts of helper T lymphocytes and killer T lymphocytes were 220/μL and 261/μL. Upon admission, a chest computed tomography (CT) scan indicated minimal bilateral pulmonary exudates. According to the aforementioned findings, the preliminary diagnosis indicated that the patient had community-acquired pneumonia. Empiric therapy with cefuroxime was initiated upon admission for prophylactic purposes. Nevertheless, the patient's pyrexia remained refractory, and there was an escalation of bilateral moist rales on the third day. Therefore, for further insights into the etiology, bronchoalveolar lavage fluid (BALF) samples were obtained through fiberoptic bronchoscopy, which revealed yellow foam-like exudates in the lungs that were positive for Gomori methenamine silver staining and displayed a small quantity of pneumocystis jirovecii encapsulation. Thus, the patient was diagnosed with PJP. The immunosuppressive agent and cefuroxime were discontinued, and caspofungin was introduced in conjunction with sulfamethoxazole (SMZ) for anti-infective purposes. Additionally, 40 mg of methylprednisolone was administered to mitigate the inflammatory response. After treatment, the patient continued to experience recurrent hyperpyrexia and dyspnea, accompanied by deterioration in vital signs. The patient's temperature was recorded at 39.4°C, heart rate was 101 beats per minute, and respiratory rate was 32 breaths per minute. Then, despite the utilization of high-flow nasal cannula (HFNC) with an oxygenation flow rate of 50 L/min and FiO_2 of 70%, as well as non-invasive positive pressure ventilation (NIPPV) with an IPAP of 18 cmH_2O, an EPAP of 8 cmH_2O, a frequency of 20 breaths/min, and FiO_2 of 90% on alternate occasions, the pO_2/FiO_2 (P/F) ratio of arterial blood gas (ABG) was 100 mmHg. The P/F value satisfied the diagnostic criteria for severe ARDS. The patient experienced an exacerbation of dyspnea, and a reexamination of chest CT revealed an aggravation of lesions in both lungs (Figure 1). On the 15th day, the patient was admitted to the ICU under consideration of PJP and severe ARDS as diagnoses. He was still under hyperpyrexia and dyspnea physical examination and laboratory data showed a deterioration of general conditions: temperature: 39.3°C, heart rate: 102 beats/min, respiratory rate: 34 breaths/min, SpO_2: 88% under high-flow nasal cannula oxygen (HFNC: oxygen flow rate of 40 L/min, FiO_2 of 60%, and blood pressure: 115/74 mmHg). Arterial blood gas analysis showed severe hypoxemia: pH: 7.41, PaO_2: 51.3 mmHg, $PaCO_2$: 29.7 mmHg, and P/F 86 mmHg. The patient was expected to require mechanical ventilation for an extended period, which significantly increased the risk of mechanical complications. Meanwhile, given the patient's desire for autonomy to manage his own behavior during dyspnea, without resorting to endotracheal intubation, coupled with the urgent need for oxygenation, the early employment of awake VV-ECMO represented the optimal course of action. With the patient's consent, the VV-ECMO was connected to him. A 15F cannula inserted through the right internal jugular vein and a 23F catheter through the right femoral vein were placed for VV-ECMO under local anesthesia. ECMO parameters (blood flow velocity: 4.5 to 5.0 L/min, gas flow rate: 4 L/min, FiO_2: 100%) were continued to be given with HFNC (Oxygen flow rate: 60 L/min, FiO_2: 50%). On the basis of SMZ treatment, meropenem (1 g q8h) combined with vancomycin (1 g q12h) was given for antimicrobial therapy, dexmedetomidine (from 0.3 μg/kg/h to 0.5 μg/kg/h) was used for shallow sedation, and remifentanil (from 0.03 μg/kg/min to 0.05 μg/kg/min) for analgesia with the purpose to smooth the dyspnea. We maintained the RASS score from −1 to 0 of shallow sedation and controlled the spontaneous breathing rate at 8–15 breaths/min for lung protection. To prevent the formation of blood clots, we employed continuous infusion of heparin and frequently monitored the patient's activated partial thromboplastin time (APTT) with the aim of maintaining a target APTT value between 60 and 80 s. Additionally, we administered enteral nutrition through a nasogastric tube to ensure a daily caloric intake of 2,100 kcal for the patient. On the 17th day, respiratory physiotherapy was initiated, which included daily use of the Portex Acapella Breathing Trainer was made at 6250 Shier Ring and sitting at the bedside with the intention of exercising respiratory muscles, preventing ICU-acquired weakness, and promoting pulmonary recruitment. On the 21st day, the manifestation of

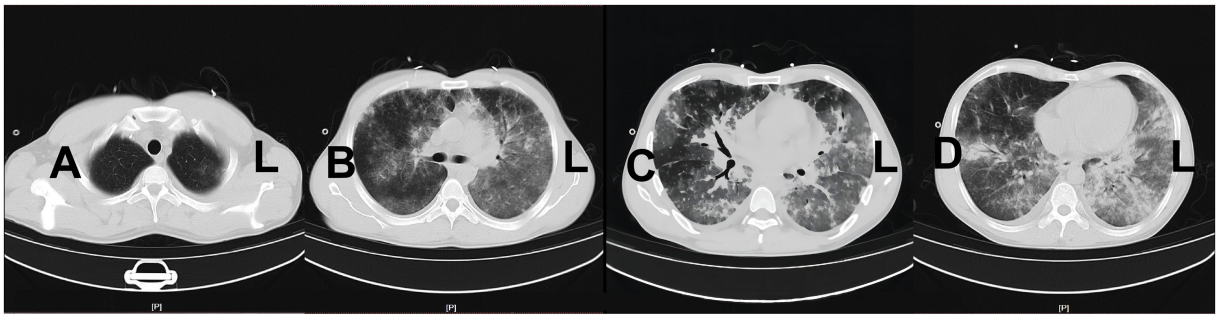


FIGURE 1
Reexamination of chest CT on the 15th day of admission before the application of ECMO.

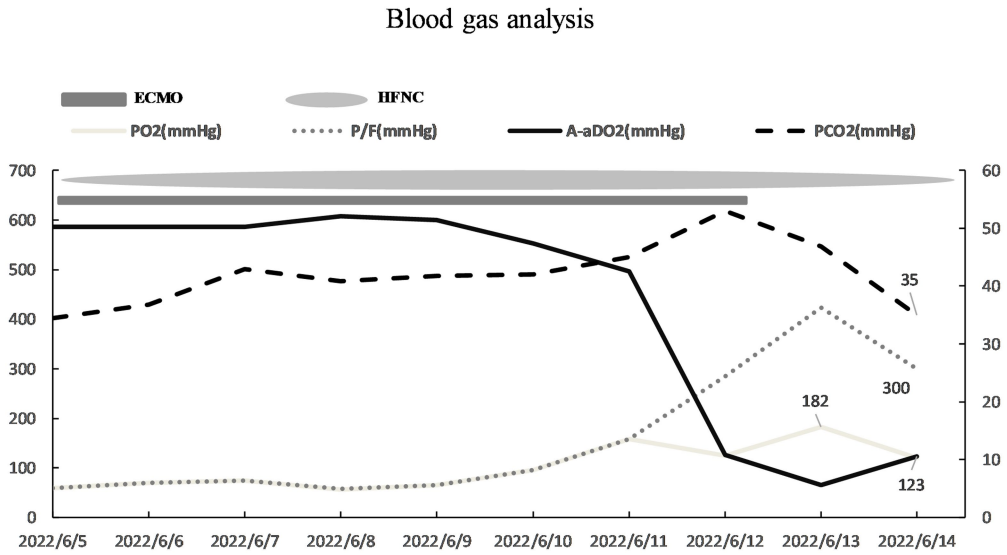


FIGURE 2
The result of blood gas analysis showed an improvement in the oxygenation index.

respiratory distress exhibited complete alleviation, the body temperature gradually regressed to the normal range, and the parameters obtained from blood gas analysis (Figure 2) as well as the radiological interpretation of the thoracic X-ray (Figure 3) depicted a gradual enhancement. According to Figure 4, the counts of NE, CRP, PCT, and IL-6 exhibited a gradual decrease over time, implying a potential amelioration or resolution of the infection. We partially adhered to the guidelines recommended by ELSO for weaning off VV-ECMO (9). We initiated a weaning trial at a PaO_2 condition of 131 mmHg on supplemental O_2 with an oxygenation flow rate of 40 L/min and FiO_2 of 45% on HFNC while the fraction of delivered oxygen (FDO_2) of VV-ECMO was 21%. Subsequently, we gradually reduced the sweep gas flow rate by 1 L/min from 5.0 L/min to our goal of 1 L/min over 4 h. Since the patient was able to tolerate the low sweep gas flow rate of VV-ECMO, we turned off the sweep gas for 4 h. Then, the arterial blood gas results obtained during the off-sweep gas trial demonstrated a PaO_2 of 125 mmHg and pH of 7.41 without any excessive work of breathing based on the patient's condition. Following an 8 h spontaneous breathing test mentioned above, the patient's P/F was 277 mmHg, leading to the withdrawal of ECMO support. The patient was finally discharged from the ICU, and the LOS in ICU was only for 7 days without any adverse and unanticipated complications.

3. Discussion

In this case, the patient, with a history of liver transplantation surgery and administration of immunosuppressant, suffered from PJP leading to severe ARDS. Both the P/F ratio of ABG and chest CT imaging confirmed the diagnosis of severe ARDS. Conventional treatments for severe ARDS include tracheal intubation, protective ventilation, prone position ventilation, and deep sedation (10). ECMO was considered as the salvage treatment. It means that the patients have to endure at least 10–14 days of mechanical ventilation in conventional therapy, which may lead to a series of mechanical ventilation-related complications such as muscle atrophy under deep sedation, diaphragmatic dysfunction, difficulty in oral care of indwelling endotracheal tubes, and inevitable ventilator-associated pneumonia (VAP) (11). PJP can be secondary to immunocompromised patients in different stations, with a rapid disease progression and high

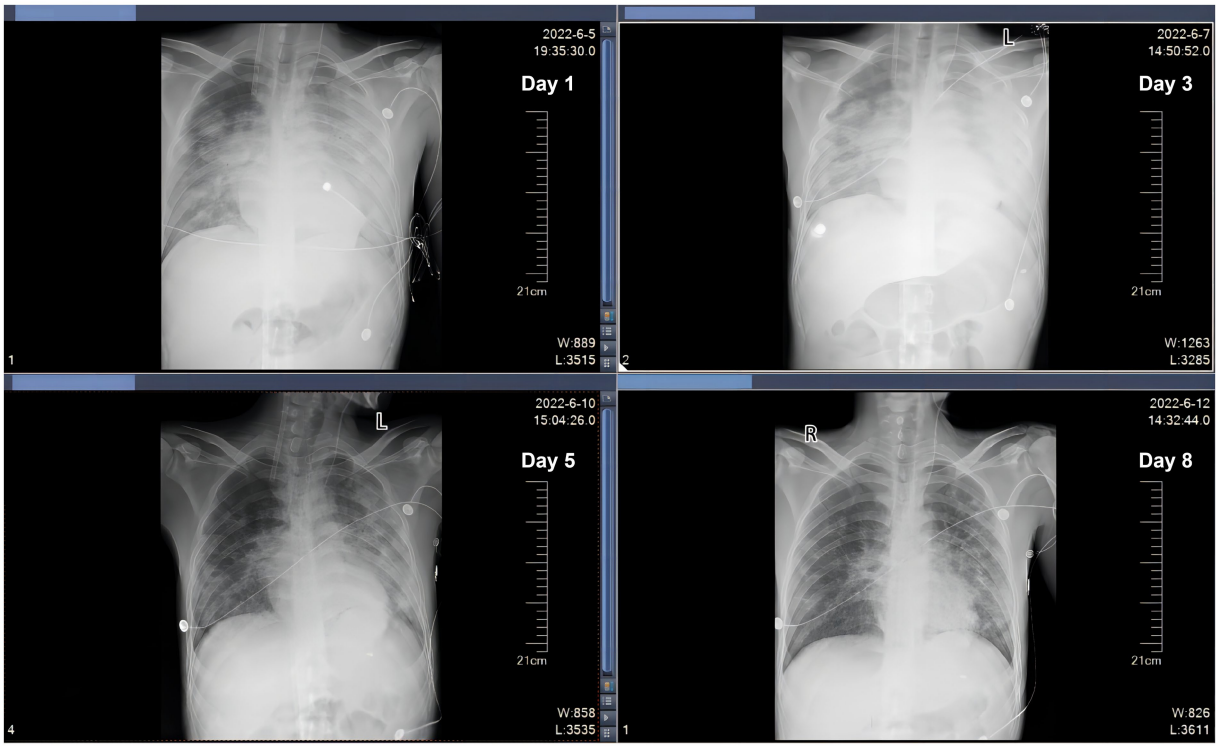


FIGURE 3
Imaging features of chest X-ray (D1, D3, D5, and D8).

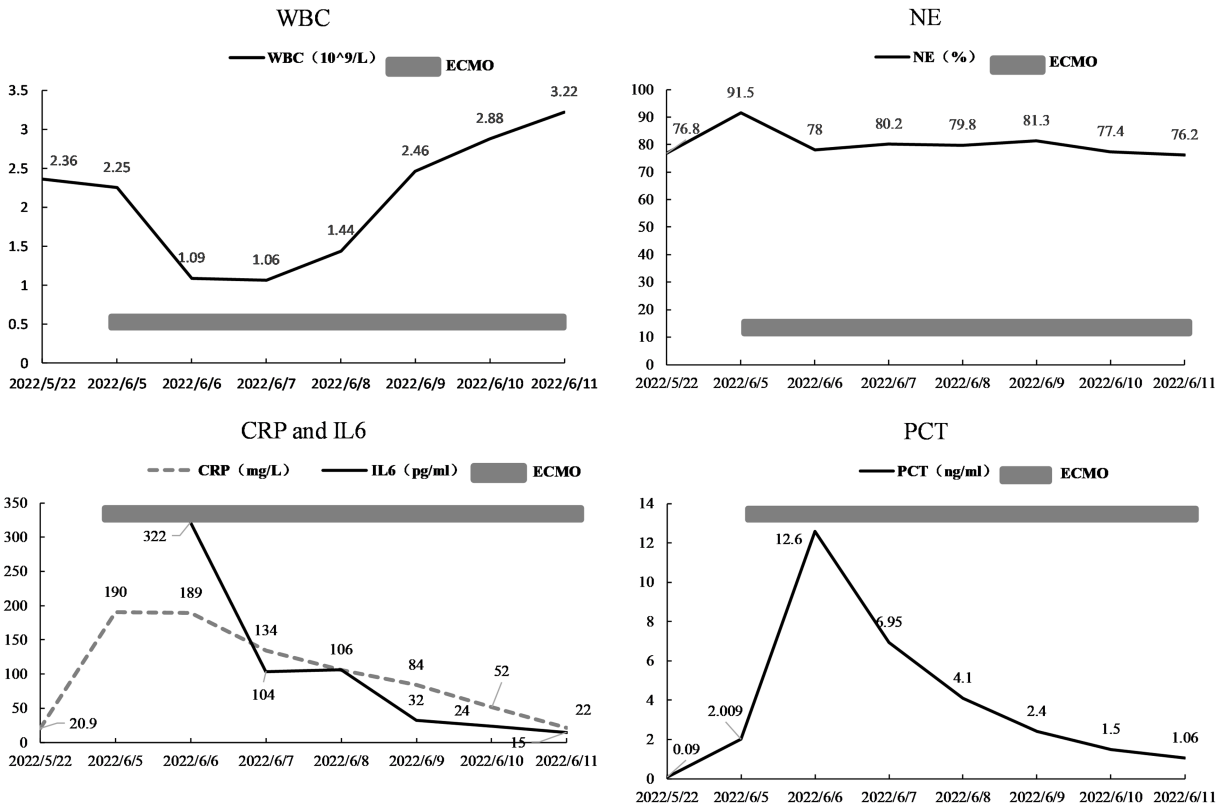


FIGURE 4
The change of WBC, NE%, CRP, IL6, and PCT.

mortality in non-HIV-infected patients (12, 13). However, the traditional mechanical ventilation treatment may induce series of complications as mentioned above. This suggests that new treatment methods and concepts need to be gradually innovated and practiced for better clinical outcomes.

In recent years, there have been several successful cases of early awake ECMO applied in different diseases, such as pulmonary hypertension, lung transplantation, broncho-cutaneous fistula, and COVID-19 (13–16). In a specific research study, patients supported with awake ECMO had higher survival rates than those primarily supported with intubated ECMO (10%, $p = 0.011$) (17). Based on the literature review and previous suggestions, awake VV-ECMO appears to be a more suitable option for individuals with isolated non-intubated lung injury, who are breathing spontaneously with severe ARDS. Thus, we innovatively applied early awake ECMO to a case of PJP complicated with severe ARDS and successfully completed the therapy due to effective management. First of all, the patient selected for the treatment was young, adherent, awake, and had few prior diseases, which reduced the complexity and risk of the treatment. At the same time, the patient's conscious state and ability to breathe spontaneously facilitated active participation of the patient in the entire treatment process, nursing care, rehabilitation exercises, psycho-social aspects, and psychological counseling, which created favorable conditions for the prompt removal of ECMO upon recovery (6). On the contrary, patients with severe ARDS who underwent invasive ventilator-assisted ventilation may encounter challenges during extubation and reintubation. These challenges are associated with prolonged mechanical ventilation duration, a significantly high ICU mortality rate of 50%, increased incidence of ventilator-associated pneumonia, heightened use of sedatives, and elevated healthcare cost (18, 19). Second, effective lung rehabilitation exercise, aimed to improve the lung volume, ventilation, and blood flow, was an important means of lung recruitment. In this case, we performed pulmonary rehabilitation exercises with early respiratory training equipment while the patient was under mild sedation. We then evaluated the effect of lung recruitment maneuvers using bedside ultrasound, electrical impedance tomography (EIT), and other methods (20). The pulmonary function, blood gas analysis, and chest X-ray imaging were observed daily while adjusting the ECMO flow rate. This helped to further evaluate lung compliance and determine the intensity of pulmonary rehabilitation treatment. Third, we meticulously complied with the prescribed protocols and guidelines to ensure stringent prevention and control of nosocomial infections within the hospital setting. Then, the implementation of meticulously administered analgesia and light sedation proved to be of utmost importance in ensuring optimal patient comfort and safety throughout the treatment process.

By carefully managing these aspects, the primary goal of lung protection was successfully achieved by effectively reducing the frequency of spontaneous breathing and mitigating the potential adverse effects associated with excessive ventilation volume caused by driving pressure. Ultimately, the patient with PJP complicated with severe ARDS secondary to immunodeficiency after liver transplantation was treated with early awake ECMO successfully for only 7 days. Importantly, this remarkable outcome was achieved without any untoward complications, such as the development of ICU-acquired weakness, catheter-related bloodstream infection, or the onset of septic shock, further highlighting the efficacy and safety of this novel treatment modality.

Undoubtedly, certain limitations were observed in this particular case. The criteria for selecting the patient limit the ability to establish the safety and efficacy of awake ECMO in elderly individuals, those with multiple comorbidities, poor compliance, or impaired consciousness. Furthermore, the unsuccessful application of awake ECMO in a severe case of H7N9 avian influenza indicates that awake and non-invasive mechanical ventilation may not always be suitable for managing severe ARDS (21). Consequently, a substantial body of clinical evidence is required to delineate the specific parameters regarding the ideal candidates, optimal timing, and appropriate methodology for implementing awake ECMO (22).

4. Conclusion

In this case, we present the effective application of awake VV-ECMO in the treatment of critically ill PJP patients, avoiding invasive mechanical ventilation. However, with the limitation outlined above, increased clinical evidence is needed to verify whether awake ECMO could be widely used in severe ARDS caused by other diseases or conditions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Shenzhen Third People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

QW: Data curation, Formal analysis, Project administration, Resources, Supervision, Visualization, Writing – original draft. FC: Investigation, Supervision, Writing – review & editing. JH: Investigation, Project administration, Resources, Supervision, Visualization, Writing – review & editing. GW: Review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The funding

for this study was provided by Shenzhen High-level Hospital Construction Fund (Nos. G2022054 and G2022120).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Martin SI, Fishman JAAST Infectious Diseases Community of Practice. Pneumocystis pneumonia in solid organ transplantation. *Am J Transplant*. (2013) 13:272–9. doi: 10.1111/ajt.12119

2. Trubin PA, Azar MM. Current concepts in the diagnosis and management of pneumocystis pneumonia in solid organ transplantation. *Infect Dis Clin N Am*. (2023) 37:617–40. doi: 10.1016/j.idc.2023.03.005

3. Coleman MH, Aldrich JM. Acute respiratory distress syndrome: ventilator management and rescue therapies. *Crit Care Clin*. (2021) 37:851–66. doi: 10.1016/j.ccc.2021.05.008

4. MacLaren G, Combes A, Brodie D. Saying no until the moment is right: initiating ECMO in the EOLIA era. *Intensive Care Med*. (2020) 46:1894–6. doi: 10.1007/s00134-020-06185-1

5. Langer T, Santini A, Bottino N, Crotti S, Batchinsky AI, Pesenti A, et al. "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. *Crit Care*. (2016) 20:150. doi: 10.1186/s13054-016-1329-y

6. Haji JY, Mehra S, Doraiswamy P. Awake ECMO and mobilizing patients on ECMO. *Indian J Thorac Cardiovasc Surg*. (2021) 37:309–18. doi: 10.1007/s12055-020-01075-z

7. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. (2016) 315:788–800. doi: 10.1001/jama.2016.0291

8. Mora-Arteaga JA, Bernal-Ramirez OJ, Rodriguez SJ. The effects of prone position ventilation in patients with acute respiratory distress syndrome. A systematic review and metaanalysis. *Med Intensiva*. (2015) 39:359–72. doi: 10.1016/j.medin.2014.11.003

9. Tonna JE, Abrams D, Brodie D, Greenwood JC, Rubio Mateo-Sidron JA, Usman A, et al. Management of adult patients supported with venovenous extracorporeal membrane oxygenation (VV ECMO): guideline from the extracorporeal life support organization (ELSO). *ASAIO J*. (2021) 67:601–10. doi: 10.1097/MAT.0000000000001432

10. Tasaka S, Ohshimo S, Takeuchi M, Yasuda H, Ichikado K, Tsushima K, et al. ARDS clinical practice guideline 2021. *Respir Investig*. (2022) 60:446–95. doi: 10.1016/j.resinv.2022.05.003

11. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. *Mayo Clin Proc*. (2017) 92:1382–400. doi: 10.1016/j.mayocp.2017.05.004

12. Wang Y, Huang X, Sun T, Fan G, Zhan Q, Weng L. Non-HIV-infected patients with pneumocystis pneumonia in the intensive care unit: a bicentric, retrospective study focused on predictive factors of in-hospital mortality. *Clin Respir J*. (2022) 16:152–61. doi: 10.1111/crj.13463

13. Wang Y, Zhou X, Saimi M, Huang X, Sun T, Fan G, et al. Risk factors of mortality from pneumocystis pneumonia in non-HIV patients: a Meta-analysis. *Front Public Health*. (2021) 9:680108. doi: 10.3389/fpubh.2021.680108

14. Camargo SM, Soder SA, Perin FA, Nascimento DZ, Schio SM. Extracorporeal membrane oxygenation in an awake patient as a bridge to lung transplantation. *J Bras Pneumol*. (2018) 44:69–70. doi: 10.1590/S1806-37562017000000125

15. Correa G, Taylor D, Vogel D, Wyncoll D. A case of broncho-cutaneous fistula secondary to tuberculosis successfully managed with awake veno-venous extracorporeal membrane oxygenation. *Respir Med Case Rep*. (2021) 32:101351. doi: 10.1016/j.rmcr.2021.101351

16. Tang J, Li W, Jiang F, Wang T. Successfully treatment of application awake extracorporeal membrane oxygenation in critical COVID-19 patient: a case report. *J Cardiothorac Surg*. (2020) 15:335. doi: 10.1186/s13019-020-01376-9

17. Stahl K, Seeliger B, Hoeper MM, David S. "Better be awake"-a role for awake extracorporeal membrane oxygenation in acute respiratory distress syndrome due to pneumocystis pneumonia. *Crit Care*. (2019) 23:418. doi: 10.1186/s13054-019-2703-3

18. Elmer J, Lee S, Rittenberger JC, Dargin J, Winger D, Emlet L. Reintubation in critically ill patients: procedural complications and implications for care. *Crit Care*. (2015) 19:12. doi: 10.1186/s13054-014-0730-7

19. Rothaar RC, Epstein SK. Extubation failure: magnitude of the problem, impact on outcomes, and prevention. *Curr Opin Crit Care*. (2003) 9:59–66. doi: 10.1097/00075198-200302000-00011

20. Bachmann MC, Morais C, Bugedo G, Bruhn A, Morales A, Borges JB, et al. Electrical impedance tomography in acute respiratory distress syndrome. *Crit Care*. (2018) 22:263. doi: 10.1186/s13054-018-2195-6

21. Xu Q, Cao Y, Jiang X, Lu W. Can awake ECMO combined with NPPV treat severe H7N9 avian influenza? A case report. *QJM*. (2019) 112:525–6. doi: 10.1093/qjmed/hcz087

22. Ding L, He H. Awake extracorporeal membrane oxygenation for acute respiratory distress syndrome, details to be defined: who, when, and how? *Crit Care Med*. (2019) 47:e1038. doi: 10.1097/CCM.0000000000003961

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 October 2023
DOI 10.3389/fmed.2023.1233518

OPEN ACCESS

EDITED BY
Jun Duan,
First Affiliated Hospital of Chongqing Medical University, China

REVIEWED BY
Carmen Silvia Valente Barbas,
University of São Paulo, Brazil
Cristian Deana,
Azienda Sanitaria Universitaria Integrata di Udine, Italy

*CORRESPONDENCE
Matthew Kheir
✉ mkheir1@northwell.edu

RECEIVED 02 June 2023
ACCEPTED 12 October 2023
PUBLISHED 31 October 2023

CITATION
Kheir M, Dong V, Roselli V and Mina B (2023) The role of ultrasound in predicting non-invasive ventilation outcomes: a systematic review.
Front. Med. 10:1233518.
doi: 10.3389/fmed.2023.1233518

The role of ultrasound in predicting non-invasive ventilation outcomes: a systematic review

Matthew Kheir[1,2]*, Vincent Dong[2,3], Victoria Roselli[4] and Bushra Mina[1,2]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Lenox Hill Hospital - Northwell Health, New York, NY, United States, [2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, United States, [3]Department of Medicine, Lenox Hill Hospital - Northwell Health, New York, NY, United States, [4]Office of Clinical Research, The Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, United States

Purpose: To systematically review and compare ultrasonographic methods and their utility in predicting non-invasive ventilation (NIV) outcomes.

Methods: A systematic review was performed using the PubMed, Medline, Embase, and Cochrane databases from January 2015 to March 2023. The search terms included the following: ultrasound, diaphragm, lung, prediction, non-invasive, ventilation, and outcomes. The inclusion criteria were prospective cohort studies on adult patients requiring non-invasive ventilation in the emergency department or inpatient setting.

Results: Fifteen studies were analyzed, which comprised of 1,307 patients ($n = 942$ for lung ultrasound score studies; $n = 365$ patients for diaphragm dysfunction studies). Lung ultrasound scores (LUS) greater than 18 were associated with NIV failure with a sensitivity 62–90.5% and specificity 60–91.9%. Similarly, a diaphragm thickening fraction (DTF) of less than 20% was also associated with NIV failure with a sensitivity 80–84.6% and specificity 76.3–91.5%.

Conclusion: Predicting NIV failure can be difficult by routine initial clinical impression and diagnostic work up. This systematic review emphasizes the importance of using lung and diaphragm ultrasound, in particular the lung ultrasound score and diaphragm thickening fraction respectively, to accurately predict NIV failure, including the need for ICU-level of care, requiring invasive mechanical ventilation, and resulting in higher rates of mortality.

KEYWORDS

non-invasive, ventilation, outcomes, lung, ultrasound, diaphragm, dysfunction

Introduction

There are several contributors in predicting the outcome of non-invasive ventilation (NIV). Historically, multiple articles have demonstrated that the prediction of noninvasive ventilation (NIV) failure was based on components of the patient's vital signs, level of consciousness, and degree of acidosis (1–6). This led to the development of a scale that considers heart rate, acidosis, consciousness, oxygenation, and respiratory rate (referred to as the HACOR scale) and is used to predict NIV failure, defined as the need for intubation after NIV intervention (7, 8). The scale was however limited in terms of predictive value in respiratory illnesses and thus an updated

HACOR score was developed that considered baseline data such as acute respiratory distress syndrome (ARDS), septic shock, immunosuppression, organ failure, among other data (9). Additional risk factors beyond the HACOR scale for NIV failure include patient baseline severity scores (SOFA, APACHE II and SAPS II), delay between admission and NIV use, duration of NIV use, patient-ventilator asynchrony, number of fiberoptic bronchoscopies performed, and increased radiographic infiltrates within the first 24 hours (5, 10–13).

Point of care ultrasound (POCUS) in the fields of pulmonary and critical care medicine has received increased attention because of its rapid availability to assess and diagnose patients, accuracy, reproducibility, low-cost profile, and lack of harmful radiation. Numerous studies have attempted to utilize various ultrasonographic methods to ultimately predict NIV outcomes. However, given the variability of each technique and the multiple sites of interest for bedside ultrasound, it is challenging to comprehend the clinical significance and the generalized acceptance of specific ultrasound modalities.

The purpose of this study is to systematically review the literature to highlight the predictiveness of bedside ultrasound with regards to NIV outcomes as well as to compare the various ultrasonographic techniques that have been used.

Materials and methods

This study was conducted in accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and the PRISMA checklist (14). A systematic review of the literature from 2015 to 2023 on the role of ultrasound in predicting NIV outcomes was performed across a 4-database wide search including PubMed, Medline, Embase, and Cochrane. The queries were performed in March 2023 with the following search terms: ultrasound, diaphragm, lung, prediction, non-invasive, ventilation, and outcomes.

Inclusion/exclusion criteria

The inclusion criteria were adults 18 years of age and older, patients in the emergency department or hospitalized, with acute respiratory failure, receiving ultrasound assessments, and on non-invasive ventilation. The exclusion criteria were studies in languages other than English, pregnant patients, post-surgical patients, patients with neuromuscular disorders, using ultrasound to determine if patient needs to be advanced to NIV, using ultrasound to evaluate if patient can be extubated or weaned from invasive mechanical ventilation, and if the study involved drug interventions. Two investigators (M.K. and V.D.) reviewed the titles and abstracts of all articles that met the inclusion and exclusion criteria, and full-text articles were obtained to verify that the criteria were met.

Results

A flow diagram documenting the method of article identification and selection is shown in Figure 1. A total of 318 studies remained after eliminating 36 duplicate studies. The investigators independently reviewed the titles and abstracts, identifying 26 full-text articles for review. Application of the inclusion and exclusion criteria yielding 15 full-text articles for inclusion in the review (15–29).

Lung ultrasound score

Several studies employ an ultrasonographic method of scoring lung pathology, namely the lung ultrasound score (LUS) (Table 1). A lung ultrasound score assessment is performed for multiple reasons, such as: perioperative oxygenation (31), predicting disease severity and mortality in ARDS (32), monitoring of lung aeration changes (after proning in ARDS, antimicrobial therapy in ventilator-associated pneumonia, selecting the ideal positive end-expiratory pressure, etc.) (33–35), weaning from mechanical ventilation (36), and as a prognosticator for respiratory failure (15, 18–20, 22, 28). There are multiple variations of the LUS, however arguably the more commonly utilized version of the LUS assessment consists of scanning a predetermined 6 regions per lung. Lung aeration of each region is graded between 0 to 3 depending on the ultrasound pattern visualized. In each region, points are allocated according to the following ultrasound pattern: normal = 0, well-defined B-lines = 1, coalescent B-lines = 2, and consolidation = 3. The total score for the LUS assessment therefore ranges from 0 to 36 (37) (Figure 2). A broader score, known as the integrated lung ultrasound score (i-LUS), was implemented during the coronavirus disease 2019 (COVID-19) pandemic that incorporates other important parameters seen with COVID-19 pneumonia. These additional parameters include: presence of pleural effusion (absent = 0, present = 1), presence of pericardial effusion (absent = 0, present = 1), measurement of IVC respiratory variation (<0–33%; absent = 0, present = 1), and diaphragm excursion (excursion >2 ± 0.5 cm was considered normal = 0, values below = 1) (18). Again, there are several other variations of the standard LUS (most of which are described in this present article) and these lung ultrasound score assessments have demonstrated positively in predicting outcomes for patients on NIV.

Ahmed et al. performed a prospective observational study of 50 ICU patients who presented with acute respiratory failure and were indicated for NIV (including COPD with exacerbation, pneumonia with no or mild secretions, acute lung injury manifested by PaO2/FiO2 < 200, and acute congestive heart failure with pulmonary edema). Lung ultrasound score, HACOR score, and serum lactate were recorded on admission and after 12 h from NIV application. To predict NIV failure, LUS with a cut-off value of 18 on admission showed sensitivity 77.0%, specificity 60.0% ($p = 0.001$). A cut-off value of 15 after 12 h NIV use showed a sensitivity of 87.0% and a specificity of 75.0% ($p < 0.001$) (15).

A similar study of 120 patients admitted for COVID-19 pneumonia showed that the optimal cutoff for the baseline LUS score was 18 (sensitivity 62%, specificity 74%). Both mortality and requirement for invasive mechanical ventilation were increased with a baseline LUS score > 18 compared to patients with baseline LUS score between 0 and 18. The hazard ratio of invasive mechanical ventilation or death for LUS score was 1.12 per point ($p = 0.0008$) (30). Dell'Aquila et al. also examined COVID-19 patients in a prospective study of 143 patients. They noted that in the survivor group, patients had a median i-LUS score of 16, while the score was 20 in the

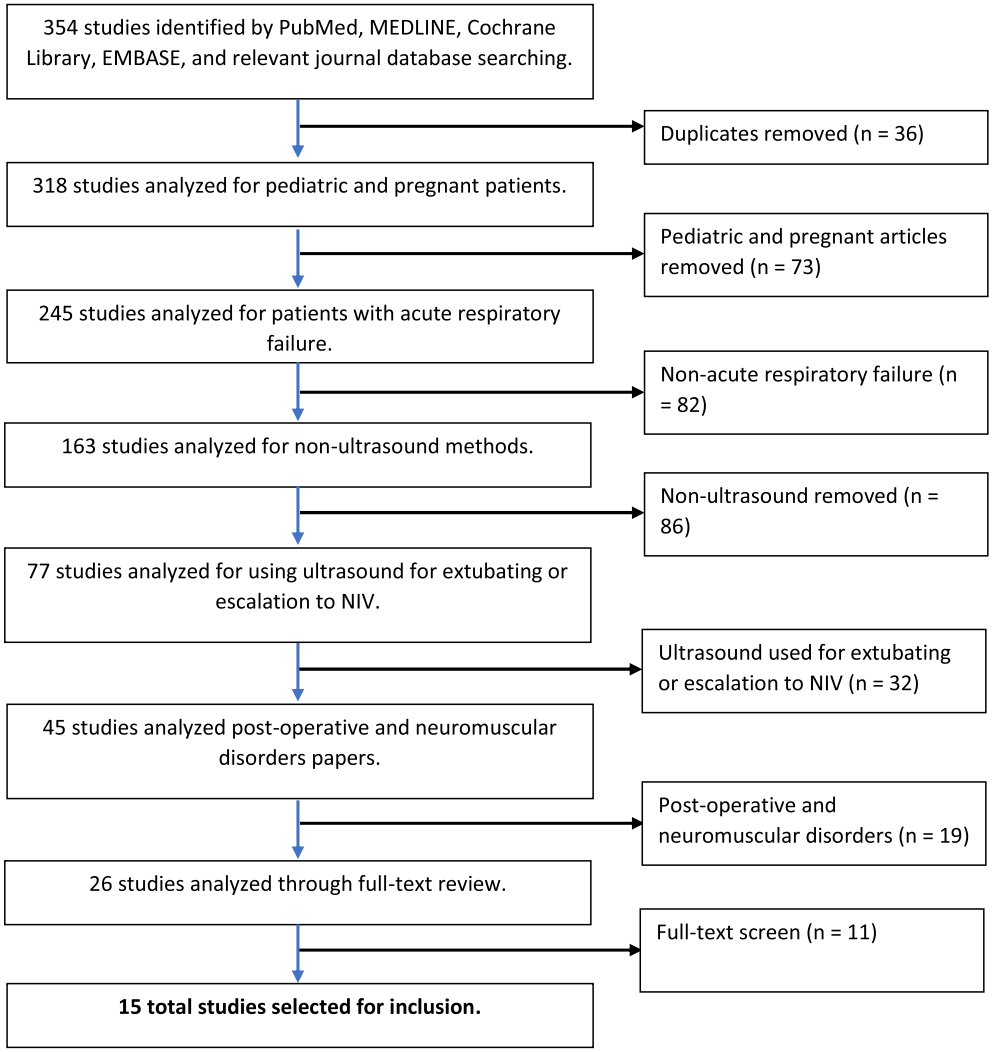


FIGURE 1
PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of literature search.

non-survivor group (interquartile range 12–20 vs. 15–24; $p = 0.005$) (18).

In a prospective cohort study of 85 patients with COVID-19 respiratory failure, Biasucci et al. showed that LUS (denoted as "LUSsc"; median score of 12 for NIV failure and median score of 6 for NIC success) as well as the amount of involved sonographic lung areas (denoted as "LUSq"; median areas involved were 6 for NIV failure and median areas involved were 3 for NIC success) were significantly higher in patients who failed NIV ($p < 0.001$) (28). This was also seen in a larger study of 280 patients with COVID-19 pneumonia by Ji et al., which demonstrated that patients with a high LUS score (defined as LUS > 12) were more likely to have poor outcomes including requiring invasive mechanical ventilation, higher incidence of ARDS, and higher mortality rates compared to the lowest LUS score group (defined as LUS 0–1), with a specificity and sensitivity of 90.5 and 91.9%, respectively (19). Blair et al. utilized the mean LUS (mLUS) score (ranging from 0 to 3) across 12 lung zones. The study revealed that every increase in mLUS score at enrollment was associated with disease progression to ICU-level of care (adjusted hazard ratio [aHR], 3.61; 95% confidence interval [CI], 1.27–10.2; $p = 0.016$) as well as 28-day mortality (aHR, 3.10; 95% CI, 1.29–7.50; $p = 0.012$) (22).

Diaphragm dysfunction

In addition to the lung ultrasound score, point of care ultrasonography can be used to rapidly assess for many pathologies including diaphragm dysfunction (DD) (Table 2). Similar to other ultrasound modalities, diaphragm-related ultrasound is noninvasive, safe, and can serve as a repeatable bedside tool. Patients with significant hypoxia who require NIV have a risk of developing diaphragmatic impairment which may poorly affect outcomes, including the need for invasive mechanical ventilation. Numerous studies have employed ultrasonography to assess functionality of the diaphragm to assist in predicting outcomes for patients on NIV (16, 17, 21, 23–27). These studies assessed diaphragm thickness (DT) or the variation of diaphragmatic thickness fraction (DTF) between end-inspiration and end-expiration. DTF is calculated from the following formula: [(Thickness at end-inspiration − Thickness at

TABLE 1 Characteristics and findings for articles utilizing lung ultrasound score.

Study/year	Country	Design/ setting/ population	Variable	Number of patients	Age (mean, standard deviation)	Male sex, %	Findings
Ji et al. (19), 2020	China	Prospective/ Hospitalized/ COVID-19 Pneumonia	LUS	280	55 (n.a.)	50.4	Patients with a high LUS score (LUS > 12) were more likely to require invasive mechanical ventilation, had higher incidence of ARDS, and had higher mortality compared to the lowest LUS score group (LUS 0–1).
Lichter et al. (30), 2020	Israel	Prospective/ Hospitalized/ COVID-19 Pneumonia	LUS	120	64.7 ± 18	62	Optimal cutoff for LUS score was 18 (Sn 62% and Sp 74%), for which both mortality and requirement for invasive mechanical ventilation were increased. Hazard ratio of IMV or death was 1.12 per LUS point.
Biasucci et al. (28), 2021	Italy	Prospective/ED/ COVID-19 Pneumonia	LUSsc and LUSq	85	64 ± 14	71.8	LUSsc and LUSq were significantly higher in patients who failed NIV than those who did not.
Ahmed et al. (15), 2022	Egypt	Prospective/ Hospitalized/ ARF	LUS	50	59 ± 13	41.4	LUS cut-off value of 18 on admission showed Sn 77.0% and Sp 60.0% of predicting NIV failure. LUS cut-off value of 15 after 12 h of NIV use showed Sn 87.0% and Sp 75.0%.
Blair et al. (22), 2022	USA	Prospective/ED and Hospitalized/ COVID-19 Pneumonia	mLUS	264	61 (n.a.)	56.8	Every incremental increase in mLUS score at enrollment was associated with an increased disease progression to ICU-level of care as well as 28-day mortality (adjusted hazard ratio of 3.61 and 3.10, respectively).
Dell'Aquila et al. (18), 2022	Italy	Prospective/ED/ COVID-19 Pneumonia	i-LUS	143	71.5 ± 14.9	59.4	Survivor group median i-LUS score of 16, while the non-survivor group score was 20 in the non-survivor group.

LUS = lung ultrasound score (12 scanning zones; ranges from 0 to 36), LUSsc = lung ultrasound score (6 scanning zones; ranges from 0 to 18), LUSq = number of involved zones on lung ultrasound (ranges from 0 to 6), mLUS = mean lung ultrasound score (12 scanning zones; ranges from 0 to 3), i-LUS (LUS score with 4 additional parameters: pleural effusion, pericardial effusion, IVC respiratory variation, and diaphragm excursion), ED, emergency department; ARF, acute respiratory failure; ARDS, acute respiratory distress syndrome; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; ICU, intensive care unit; Sn, Sensitivity; Sp, specificity.

end-expiration)/(Thickness at end expiration)] × 100, see Figure 3. A DTF, also known as change in diaphragmatic thickness (ΔTdi), <20% is consistent with diaphragmatic dysfunction (39) (Figure 4). For sake of consistency, this article will use the term DTF with knowledge that it is interchangeable with ΔTdi.

Across the more recent studies which are highlighted in this article, diaphragm evaluation was performed on patients with an acute exacerbation of COPD (AECOPD) or with acute respiratory failure from SARS-COV2 infection. Marchioni et al. performed a prospective observational study using ultrasound to assess diaphragm dysfunction in patients with AECOPD and reported that patients with diaphragmatic dysfunction had a higher risk for NIV failure than those without DD (risk ratio = 4.4; $p < 0.001$). Change in diaphragm thickness (DTF) <20% during tidal volume was the predefined cutoff for identifying DD. The study investigated the correlation between ultrasound-assessed DD and the transdiaphragmatic pressure (Pdi) assessed using an invasive sniff maneuver [esophageal pressure (Pes) and gastric pressure (Pga) levels are recorded using balloon catheters before starting NIV; transdiaphragmatic generating pressure capacity (Pdi) was obtained

TABLE 2 Characteristics and findings for articles utilizing diaphragm dysfunction.

Study/year	Country	Design/ setting/ population	Variable	Number of patients	Age (mean, standard deviation)	Male sex, %	Findings
Antenora et al. (21), 2016	Italy	Prospective/ Hospitalized/ AECOPD	DTF	41	76 (n.a.)	63.4	The presence of DTF < 20% on admission was associated with NIV failure, increased stay in ICU, prolonged use of IMV and a higher mortality rate.
Marchioni et al. (17), 2018	Italy	Prospective/ Hospitalized/ AECOPD	DTF	75	78 (n.a.)	51	Patients with a DTF < 20% have significantly higher risk of NIV failure and mortality (risk ratio = 4.4).
Cammarota et al. (27), 2019	Italy	Prospective/ED/ AECOPD	DT and DE	22	Median age 79	38	Diaphragmatic excursion assessment 2 h after NIV initiation was a better predictor of NIV failure than left expiratory diaphragmatic thickness, pH, and paCO2 (NIV success 1.99 cm vs. NIV failure 1.20 cm excursion).
Corradi et al. (23), 2020	Italy	Prospective/ Hospitalized/ COVID-19 Pneumonia	DTF	27	Median age 66	85	NIV failure significantly associated with low DTF. The best DTF threshold for predicting NIV failure was 21.4% with Sn 94.4% and Sp 88.9%.
Barbariol et al. (29), 2021	Italy	Prospective/ Hospitalized/De-novo ARF	DE	47	65.5 ± 14.8	57.4	NIV failure associated with low DE (not statistically significant). As a predictor for NIV outcomes, DE had an AUC 0.53 with a Sn 58.1% and Sp 62.5%.
Corradi et al. (23), 2021	Italy	Prospective/ Hospitalized/ COVID-19 Pneumonia	DT	77	Median age 59	66.2	Individuals who developed adverse outcomes on NIV had thinner diaphragms than those who did not (2.0 vs. 2.2 mm).
Kocyigit et al. (24), 2021	Turkey	Prospective/ED/ AECOPD	DTF	60	70.9 ± 8.8	78.3	DTF < 20% has Sn 84.6% and Sp 91.5% in predicting NIV failure.
Mercurio et al. (26), 2021	Italy	Prospective/ED/ De-novo ARF	DTF	18	66 ± 19	44.5	DTF < 36.3% significantly predicted NIV failure with Sn 71.7% and Sp 94.3%.
Elsayed et al. (16), 2022	Egypt	Prospective/ Hospitalized/ AECOPD	DTF	75	59.3 ± 10.1	85.3	DTF < 26–29% on both sides (left hemidiaphragm% - right hemidiaphragm%) had Sn 96.67% and Sp 80–82.22% in predicting NIV failure.

DT, diaphragm thickness; DE, diaphragmatic excursion; DTF, diaphragm thickness fraction; DTF formula, [(Thickness at end-inspiration – Thickness at end-expiration)/(Thickness at end expiration)] × 100; AECOPD, acute exacerbation of COPD; ED, emergency department; ARF, acute respiratory failure; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; ICU, intensive care unit; Sn, Sensitivity; Sp, specificity.

by subtracting Pes from Pga (Pga – Pes) during a sniff maneuver], see Figure 5. It was reported that DTF highly correlated and had similar accuracy in identifying diaphragmatic dysfunction as with Pdi sniff (Pearson's $r = 0.81$; $p = 0.004$). Lastly, the study demonstrated that DTF < 20% had better accuracy in predicting NIV failure than baseline pH value <7.25, as well as early changes in arterial pH and PaCO2 following initiation of NIV (AUCs 0.84, 0.51, 0.56, and 0.54, respectively; $p < 0.0001$) (17).

Cammarota et al. similarly reported diaphragmatic excursion assessment 2 h after NIV initiation was a better predictor of NIV failure than pH, PaCO2, and left expiratory diaphragmatic thickness. Diaphragmatic excursion was greater in NIV successes than in NIV

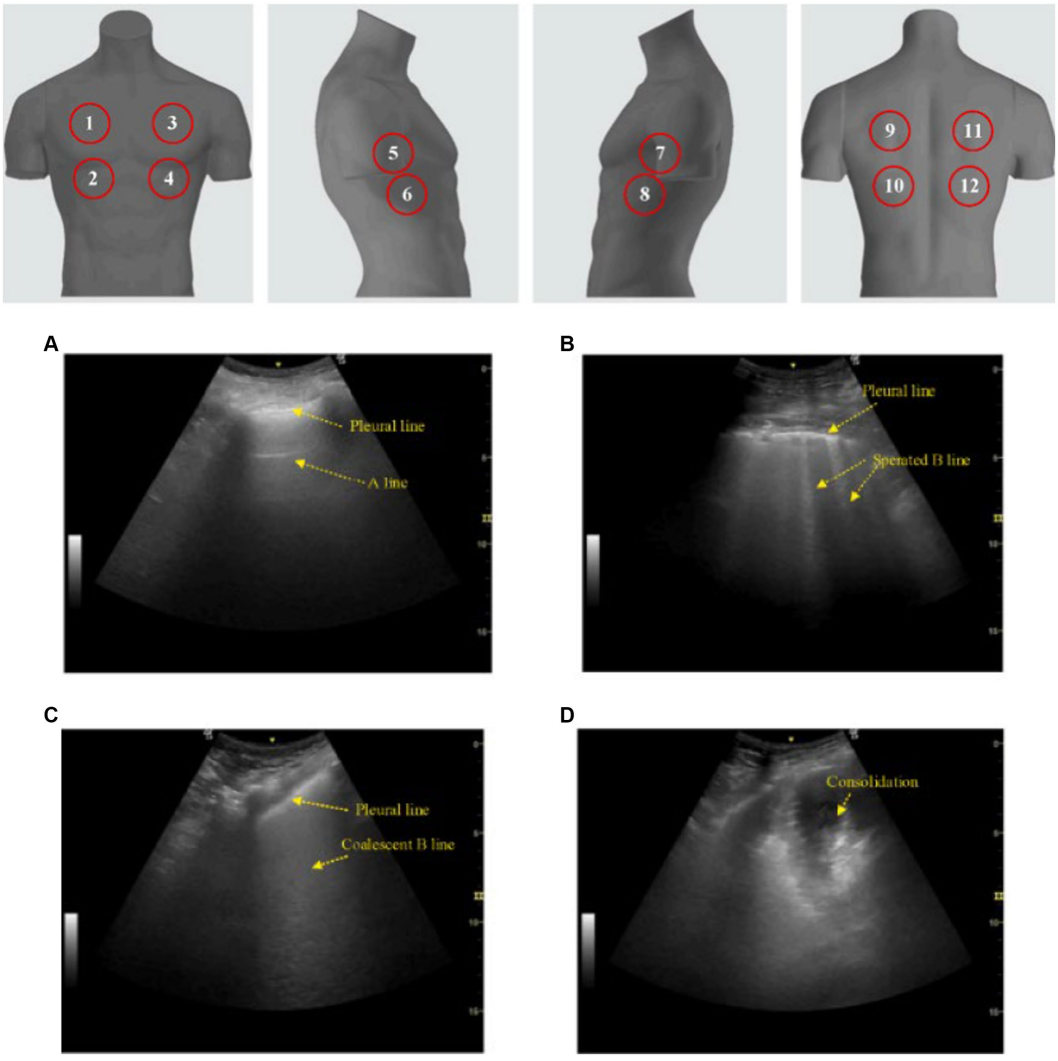


FIGURE 2
Lung ultrasound score (LUS). The classic LUS requires scanning 12 zones (upper image; 6 on each hemithorax) while scoring each zone from 0 to 3 based on pattern. **(A)** A score of 0 is a normal pattern. **(B)** A score of 1 requires at minimum 3 isolated or coalescent B-lines covering <50% of the screen without clear subpleural alterations. **(C)** A score of 2 is given when B-lines encompass >50% of the screen without clear subpleural alterations. **(D)** And finally, a score of 3 is made when consolidation is observed. Total scores range from 0 to 36. This image is reproduced with permission from the Elsevier Novel Coronavirus Center. No changes were made to this image (38).

failures at initiation of NIV (1.92 [1.22–2.54] cm vs. 1.00 [0.60–1.41] cm, $p = 0.02$) and at 2 h after initiation of NIV (1.99 [1.63–2.54] cm vs. 1.20 [0.79–1.41] cm, $p = 0.008$), respectively (27). Diaphragmatic dysfunction was also evaluated through diaphragmatic excursion by Barbariol et al. in ICU patients admitted for acute respiratory failure. Data was collected right before starting NIV as well as 1 h after initiating NIV. Diaphragmatic dysfunction was defined as a diaphragmatic excursion of less than 1.00 cm. Out of 47 patients, the patients without diaphragmatic dysfunction had about a 10% increase in NIV success than patients with diaphragmatic dysfunction, which was not statistically significant ($p = 0.54$). They also performed ROC analysis and noted that when using diaphragmatic excursion as a predictor of NIV response the area under the curve was 0.53; the best sensitivity (58.1%) and specificity (62.5%) was obtained with a diaphragmatic excursion cut-off of 1.37 cm (29).

Elsayed et al. conducted a prospective observational study where patients with acute exacerbation of COPD (AECOPD) were categorized into successful and failed NIV groups and DTF was measured. Readings of DTF in the successful NIV group were ≥ 33–38% ($p < 0.001$) while failed NIV had DTF values ≤16–18% ($p < 0.001$). In addition, cut-off value of DTF < 26–29% on both sides (left hemidiaphragm% - right hemidiaphragm%) was associated with NIV failure with 96.67% sensitivity, 80–82.22% specificity, 76.3–78.4% positive predictive value (PPV), and a 97.3–97.4% negative predictive value (NPV) (16). In a similar study by Kocyigit et al. on patients with AECOPD in the emergency department, DD (defined as DTF of <20% during spontaneous breathing) had a high sensitivity of 84.6% (95% CI:54.6–98.1), specificity of 91.5% (95% CI:79.6–97.6), PPV 73.3% (95% CI:51.2–87.8), and NPV 95.6% (95% CI:85.7–98.7) (24). Antenora et al. underwent a pilot study on the prevalence and clinical consequences of diaphragmatic dysfunction diagnosed by

$$DTF = \frac{(Thickness\ at\ end\ inspiration) - (Thickness\ at\ end\ expiration)}{Thickness\ at\ end\ expiration}\ x\ 100$$

FIGURE 3
Equation for diaphragm thickness fraction (DTF).

ultrasonography during AECOPD and reported that DD (defined as DTF < 20% during spontaneous breathing) was found to be strongly correlated with NIV failure ($p < 0.001$, $R^2 = 0.27$), longer ICU stay ($p = 0.02$, $R^2 = 0.13$), prolonged mechanical ventilation ($p = 0.023$, $R^2 = 0.15$), and need for tracheostomy ($p = 0.006$, $R^2 = 0.20$) (21). In a study by Mercurio et al. on patients with de-novo acute respiratory failure, cut-off values for DTF were explored that would accurately predict NIV failure. It was determined that the cut-off value of DTF < 36.3% significantly predicted NIV failure ($p < 0.0001$) with sensitivity of 71.7% (95% CI 56.5–84.0) and specificity of 94.3% (95% CI 80.8–99.3) (26).

In SARS-COV2 patients, Corradi et al. underwent a single-center pilot study that reported in their univariate logistic regression analysis that CPAP failure was significantly associated with a low DTF (odds ratio [OR]: 0.673; $p < 0.001$) and high respiratory rate (OR: 1.572; $p < 0.001$), but only DTF reached statistical significance at multivariate analysis (OR: 0.681; $p < 0.001$) (23). The same investigators performed a separate study and noted that patients on NIV who developed adverse outcomes had thinner diaphragms than those who did not (2.0 vs. 2.2 mm, $p = 0.001$) (25).

Discussion

Predicting NIV failure remains a diagnostic dilemma in general practice. Recent literature shows that patients presenting with acute respiratory failure have an NIV failure rate around 31–50% with nearly 65% of NIV failures occurring within 1–48 h of NIV use (8, 42–44). Current methods of evaluating for impending NIV failure is based on a multitude of parameters, of which some include monitoring vital signs, evaluating for signs of respiratory distress on physical examination, obtaining arterial blood gas values, calculating severity scores (e.g., SOFA, APACHE II, etc.), serial chest radiographs, and so forth (3, 6–9, 13, 43, 45). Undoubtedly these measures are crucial, but ongoing monitoring and the time required to obtain all this information can be tedious and laborious. The main findings of this systematic review emphasize the effective ability of utilizing bedside ultrasound as a potential *independent* predictive tool for NIV outcomes.

This study demonstrates that point of care ultrasound of the lung (e.g., lung ultrasound score) and diaphragm (e.g., diaphragm thickening fraction) can predict NIV failure early on (15–19, 21–30). This is pivotal as a delay in early detection of potential NIV failure has been shown to increase length of hospital stay, delay endotracheal intubation and increase hospital morbidity and mortality (45–48). Also, this may serve as an additional tool in guiding clinicians when considering patient disposition with regard to deciding escalating level of monitoring to an intermediate care unit (i.e., stepdown unit) vs. an intensive care unit. Clinicians may also use these ultrasound tools to communicate with family members and/or healthcare proxies about suspected outcomes for the patient. Additionally, clinicians may use this information to proactively prepare for anticipated outcomes of NIV failure (such as longer ICU stay, prolonged mechanical ventilation, mortality, and need for tracheostomy) by either providing closer patient monitoring or even considering additional treatment modalities. A recent emergency department study evaluating COVID-19 patients showed that LUS improved prognostic stratification over clinical judgment alone and supported standardized disposition decisions (49).

In a more pragmatic way of interpreting these articles, one may suggest based on these findings that perhaps a lung ultrasound score greater than 18 (out of 36 total) in a patient places the individual at a higher risk for NIV failure (e.g., ICU admission, invasive mechanical ventilation, and mortality). Likewise, a low diaphragm thickness fraction (also known as change in diaphragm thickness) accurately predicts diaphragm dysfunction. A corresponding DTF value of less than 20% highly correlates with NIV failure. Diaphragm thickness and diaphragmatic excursion were evaluated in three of the nine diaphragm ultrasound studies that met inclusion criteria (25, 27, 29). The two studies in this review examining diaphragmatic excursion showed mixed results in terms of predicting NIV failure, whereas one of those studies concluded that diaphragm thickness was a better predictor of NIV outcomes compared to diaphragmatic excursion. The inconsistency of the results and lack of studies evaluating these two variables, diaphragm thickness and diaphragmatic excursion, make it difficult to interpret and utilize these ultrasonographic methods clinically. Currently, additional research is required to evaluate these ultrasound techniques in the setting of predicting NIV outcomes.

Although the outcomes of many of these studies are promising and exemplify the independent utility of performing bedside ultrasound to predict NIV failure, there are some limitations. Firstly, all of the aforementioned studies are small unblinded prospective observational studies and many are conducted at a single institution. In addition, a vast majority of these studies focus on acute respiratory failure from either COVID-19 or AECOPD, which decreases generalizability to other patient populations (e.g., congestive heart failure, post-operative, bacterial pneumonia, etc.). Moreover, the timing of the ultrasound evaluation and the treatment course of the patients are not standardized, making the external validity of the results difficult to establish. There were also many lung ultrasound scoring systems (e.g., LUS, mLUS, i-LUS, etc.) and different cut-off values for both LUS and DTF to determine the same outcomes. This heterogeneity makes it difficult to perform a pooled analysis. Finally, there were unfortunately only two studies that fit the inclusion criteria that examined diaphragmatic thickness and two studies that examined diaphragmatic excursion as predictors for NIV failure. Hence, much of the conversation regarding diaphragmatic dysfunction centered on the diaphragm thickening fraction instead.

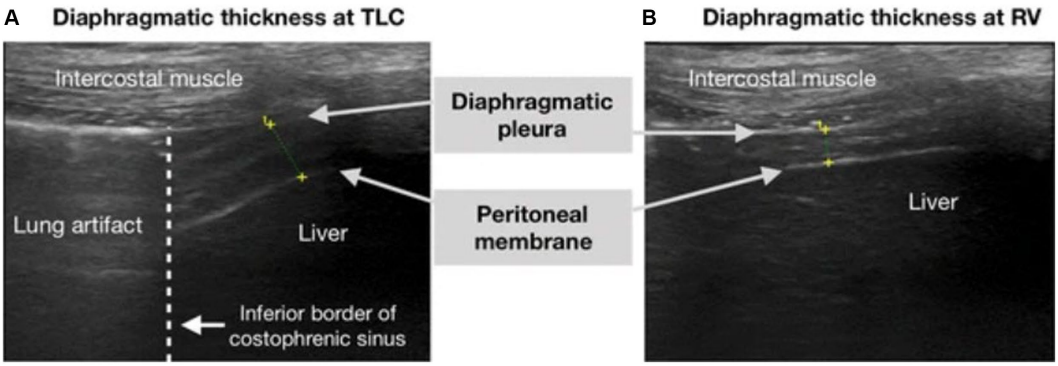


FIGURE 4
Obtaining diaphragm thickness fraction on ultrasound. Ultrasound image of the diaphragm on B-mode, showing the three layers of the diaphragm (hypoechoic diaphragm bordered by hyperechoic diaphragmatic pleura and the peritoneal membrane). Seen in **(A)** total lung capacity (TLC) and **(B)** residual volume, which is equivalent to end-inspiration and end-expiration, respectively. This image was reproduced with the permission of the Creative Commons license. No changes were made to this image. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to this image (41).

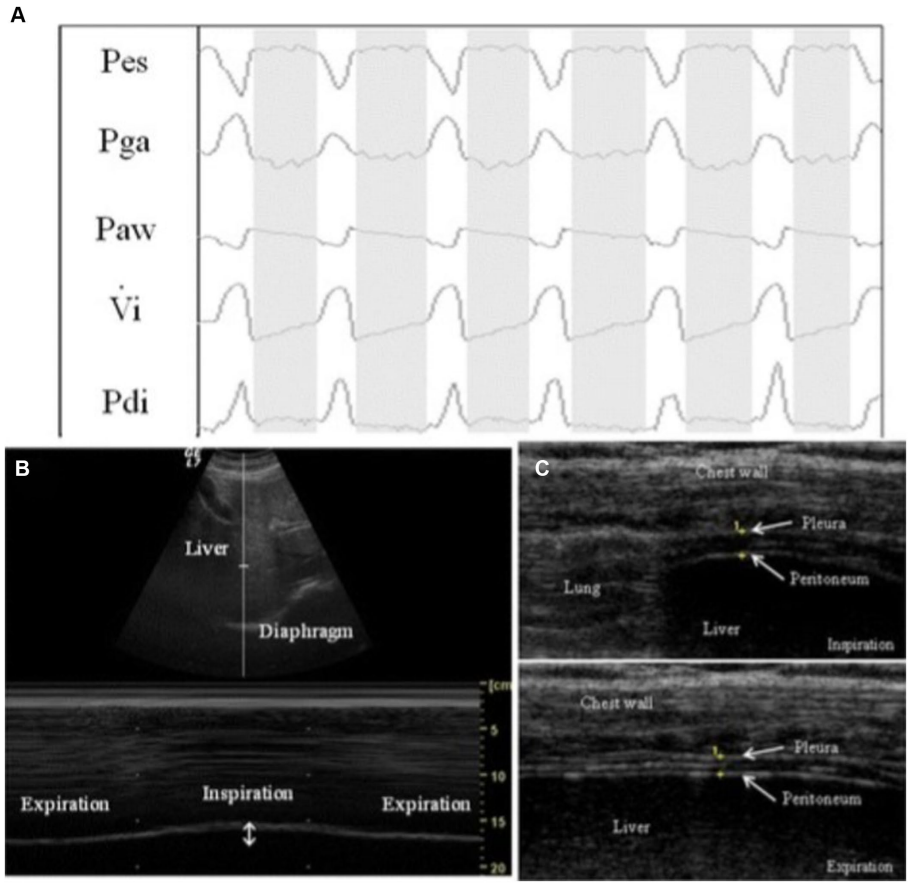


FIGURE 5
Example of respiratory tracings with ultrasound measurements during a pressure support of 0 cm H_2O (PS_0 step). **(A)** Respiratory tracings showing: Pes, esophageal pressure; Pga, gastric pressure; Paw, airway pressure; Vi, respiratory flow; Pdi, transdiaphragmatic pressure. The white columns represent inspiration and gray columns represent expiration phases. **(B)** Ultrasound view of diaphragm excursion during spontaneous breathing in B-mode (upper) and M-mode (lower). **(C)** Ultrasound view of the diaphragm in the zone of apposition during inspiration (upper) and during expiration (lower). The diaphragm is the three-layer structure in the middle consisting of a hypoechoic central layer sounded by an echogenic diaphragmatic pleurae and peritoneum, as indicated by the yellow arrows. This image was adopted with the permission of the Creative Commons license. No changes were made to this image. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to this image (40).

Conclusion

The results of this systematic review emphasize the clinical utility of performing bedside ultrasonography to predict non-invasive ventilation outcomes. Lack of early recognition of impending NIV failure in patients can be deleterious as these individuals often require ICU admission, invasive mechanical ventilation, and have higher mortality rates. Both the LUS and DTF (i.e., indicators of lung parenchymal injury and diaphragmatic dysfunction, respectively) have been shown to accurately predict NIV outcomes. Further larger prospective cohort studies are warranted to contribute to standardizing LUS and DTF across a wide range of etiologies of acute respiratory failure. Moreover, additional investigations are necessary to evaluate whether a combination of the LUS, DTF, and HACOR score can best predict NIV outcomes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

MK and BM: conceptualization. MK, VD, and BM: methodology and writing – review and editing. MK and VD: investigation, data curation, and original draft preparation. MK and VR: image contributions. BM: visualization and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med*. (2007) 35:18–25. doi: 10.1097/01.CCM.0000251821.44259.F3

2. Nicolini A, Ferraioli G, Ferrari-Bravo M, Barlascini C, Santo M, Ferrera L. Early non-invasive ventilation treatment for respiratory failure due to severe community-acquired pneumonia. *Clin Respir J*. (2016) 10:98–103. doi: 10.1111/crj.12184

3. Yoshida Y, Takeda S, Akada S, Hongo T, Tanaka K, Sakamoto A. Factors predicting successful noninvasive ventilation in acute lung injury. *J Anesth*. (2008) 22:201–6. doi: 10.1007/s00540-008-0637-z

4. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. *Crit Care*. (2006) 10:R79. doi: 10.1186/cc4923

5. Carrillo A, Gonzalez-Diaz G, Ferrer M, Martinez-Quintana ME, Lopez-Martinez A, Llamas N, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med*. (2012) 38:458–66. doi: 10.1007/s00134-012-2475-6

6. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, Confalonieri M, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med*. (2001) 27:1718–28. doi: 10.1007/s00134-001-1114-4

7. Duan J, Han X, Bai L, Zhou L, Huang S. Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. *Intensive Care Med*. (2017) 43:192–9. doi: 10.1007/s00134-016-4601-3

8. Duan J, Wang S, Liu P, Han X, Tian Y, Gao F, et al. Early prediction of noninvasive ventilation failure in COPD patients: derivation, internal validation, and external validation of a simple risk score. *Ann Intensive Care*. (2019) 9:108. doi: 10.1186/s13613-019-0585-9

9. Duan J, Chen L, Liu X, Bozbay S, Liu Y, Wang K, et al. An updated HACOR score for predicting the failure of noninvasive ventilation: a multicenter prospective observational study. *Crit Care*. (2022) 26:196. doi: 10.1186/s13054-022-04060-7

10. Di Marco F, Centanni S, Bellone A, Messinesi G, Pesci A, Scala R, et al. Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomized controlled trial. *Crit Care*. (2011) 15:R283. doi: 10.1186/cc10567

11. Demoule A, Girou E, Richard J-C, Taille S, Brochard L. Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med*. (2006) 32:1756–65. doi: 10.1007/s00134-006-0324-1

12. Riviere S, Monconduit J, Zarka V, Massabie P, Boulet S, Dartevelle P, et al. Failure of noninvasive ventilation after lung surgery: a comprehensive analysis of incidence and possible risk factors. *Eur J Cardiothorac Surg*. (2011) 39:769–76. doi: 10.1016/j.ejcts.2010.08.016

13. Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med*. (2008) 36:2766–72. doi: 10.1097/CCM.0b013e31818699f6

14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

15. Ahmed WMK, Samir M, Andraos AW, Hosny M. Radiological and clinical perspectives to predict failure of non-invasive ventilation in acute respiratory failure. *Egypt J Crit Care Med*. (2022). doi: 10.1097/EJ9.0000000000000047

16. Elsayed AA, Neanaa EHM, Beshey BN. Diaphragmatic impairment as a predictor of invasive ventilation in acute exacerbation of chronic obstructive pulmonary disease patients. *Egypt J Anaesth*. (2022) 38:334–41. doi: 10.1080/11101849.2022.2085975

17. Marchioni A, Castaniere I, Tonelli R, Fantini R, Fontana M, Tabbì L, et al. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. *Crit Care*. (2018) 22:109. doi: 10.1186/s13054-018-2033-x

18. Dell'Aquila P, Raimondo P, Racanelli V, de Luca P, de Matteis S, Pistone A, et al. Integrated lung ultrasound score for early clinical decision-making in patients with COVID-19: results and implications. *Ultrasound J*. (2022) 14:21. doi: 10.1186/s13089-022-00264-8

19. Ji L, Cao C, Gao Y, Zhang W, Xie Y, Duan Y, et al. Prognostic value of bedside lung ultrasound score in patients with COVID-19. *Crit Care*. (2020) 24:700. doi: 10.1186/s13054-020-03416-1

20. Yasukawa K, Minami T, Boulware DR, Shimada A, Fischer EA. Point-of-care lung ultrasound for COVID-19: findings and prognostic implications from 105 consecutive patients. *J Intensive Care Med*. (2021) 36:334–42. doi: 10.1177/0885066620988831

21. Antenora F, Fantini R, Iattoni A, Castaniere I, Sdanganelli A, Livrieri F, et al. Prevalence and outcomes of diaphragmatic dysfunction assessed by ultrasound technology during acute exacerbation of COPD: a pilot study. *Respirology*. (2017) 22:338–44. doi: 10.1111/resp.12916

22. Blair PW, Siddharthan T, Liu G, Bai J, Cui E, East J, et al. Point-of-care lung ultrasound predicts severe disease and death due to COVID-19: a prospective cohort study. *Crit Care Explor*. (2022) 4:e0732. doi: 10.1097/CCE.0000000000000732

23. Corradi F, Vetrugno L, Orso D, Bove T, Schreiber A, Boero E, et al. Diaphragmatic thickening fraction as a potential predictor of response to continuous positive airway pressure ventilation in Covid-19 pneumonia: a single-center pilot study. *Respir Physiol Neurobiol*. (2021) 284:103585. doi: 10.1016/j.resp.2020.103585

24. Kocyigit H, Gunalp M, Genc S, Oguz AB, Koca A, Polat O. Diaphragm dysfunction detected with ultrasound to predict noninvasive mechanical ventilation failure: a prospective cohort study. *Am J Emerg Med*. (2021) 45:202–7. doi: 10.1016/j.ajem.2020.08.014

25. Corradi F, Isirdi A, Malacarne P, Santori G, Barbieri G, Romei C, et al. Low diaphragm muscle mass predicts adverse outcome in patients hospitalized for COVID-19 pneumonia: an exploratory pilot study. *Minerva Anestesiol*. (2021) 87:432–8. doi: 10.23736/S0375-9393.21.15129-6

26. Mercurio G, D'Arrigo S, Moroni R, Grieco DL, Menga LS, Romano A, et al. Diaphragm thickening fraction predicts noninvasive ventilation outcome: a preliminary physiological study. *Crit Care*. (2021) 25:219. doi: 10.1186/s13054-021-03638-x

27. Cammarota G, Sguazzotti I, Zanoni M, Messina A, Colombo D, Vignazia GL, et al. Diaphragmatic ultrasound assessment in subjects with acute Hypercapnic respiratory failure admitted to the emergency department. *Respir Care*. (2019) 64:1469–77. doi: 10.4187/respcare.06803

28. Biasucci DG, Buonsenso D, Piano A, Bonadia N, Vargas J, Settanni D, et al. Lung ultrasound predicts non-invasive ventilation outcome in COVID-19 acute respiratory failure: a pilot study. *Minerva Anestesiol*. (2021) 87:1006–16. doi: 10.23736/S0375-9393.21.15188-0

29. Barbariol F, Deana C, Guadagnin GM, Cammarota G, Vetrugno L, Bassi F. Ultrasound diaphragmatic excursion during non-invasive ventilation in ICU: a prospective observational study. *Acta Biomed*. (2021) 92:e2021269. doi: 10.23750/abm.v92i3.11609

30. Lichter Y, Topilsky Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Lung ultrasound predicts clinical course and outcomes in COVID-19 patients. *Intensive Care Med*. (2020) 46:1873–83. doi: 10.1007/s00134-020-06212-1

31. Patel SK, Bansal S, Puri A, Taneja R, Sood N. Correlation of perioperative atelectasis with duration of anesthesia, pneumoperitoneum, and length of surgery in patients undergoing laparoscopic cholecystectomy. *Cureus*. (2022) 14:e24261. doi: 10.7759/cureus.24261

32. Skopljanac I, Ivelja MP, Barcot O, Brdar I, Dolic K, Polasek O, et al. Role of lung ultrasound in predicting clinical severity and fatality in COVID-19 pneumonia. *J Pers Med*. (2021) 11:757. doi: 10.3390/jpm11080757

33. Heldeweg MLA, Mousa A, van Ekeren J, Lieveld AWE, Walburgh-Schmidt RS, Smit JM, et al. Lung ultrasound to predict gas-exchange response to prone positioning in COVID-19 patients: a prospective study in pilot and confirmation cohorts. *J Crit Care*. (2023) 73:154173. doi: 10.1016/j.jcrc.2022.154173

34. Ammar MA, Hilal A, Abdalla W. The role of lung ultrasound in procalcitonin-guided antibiotic discontinuation in ventilator-associated pneumonia. *Indian J Anaesth*. (2022) 66:431–5. doi: 10.4103/ija.ija_989_21

35. Tang K-Q, Yang S-L, Zhang B, Liu H-X, Ye D-Y, Zhang H-Z, et al. Ultrasonic monitoring in the assessment of pulmonary recruitment and the best positive end-expiratory pressure. *Medicine (Baltimore)*. (2017) 96:e8168. doi: 10.1097/MD.0000000000008168

36. Soliman SB, Ragab F, Soliman RA, Gaber A, Kamal A. Chest ultrasound in predication of weaning failure. *Open Access Maced J Med Sci*. (2019) 7:1143–7. doi: 10.3889/oamjms.2019.277

37. Dargent A, Chatelain E, Si-Mohamed S, Simon M, Baudry T, Kreitmann L, et al. Lung ultrasound score as a tool to monitor disease progression and detect ventilator-associated pneumonia during COVID-19-associated ARDS. *Heart Lung*. (2021) 50:700–5. doi: 10.1016/j.hrtlng.2021.05.003

38. Xing W, He C, Li J, Qin W, Yang M, Li G, et al. Automated lung ultrasound scoring for evaluation of coronavirus disease 2019 pneumonia using two-stage cascaded deep learning model. *Biomed Signal Process Control*. (2022) 75:103561. doi: 10.1016/j.bspc.2022.103561

39. Ali ER, Mohamad AM. Diaphragm ultrasound as a new functional and morphological index of outcome, prognosis and discontinuation from mechanical ventilation in critically ill patients and evaluating the possible protective indices against VIDD. *Egypt J Chest Dis Tuberculosis*. (2017) 66:339–51. doi: 10.1016/j.ejcdt.2016.10.006

40. Umbrello M, Formenti P, Longhi D, Galimberti A, Piva I, Pezzi A, et al. Diaphragm ultrasound as indicator of respiratory effort in critically ill patients undergoing assisted mechanical ventilation: a pilot clinical study. *Crit Care*. (2015) 19:161. doi: 10.1186/s13054-015-0894-9

41. Pirompanich P, Romsaiyut S. Use of diaphragm thickening fraction combined with rapid shallow breathing index for predicting success of weaning from mechanical ventilator in medical patients. *J Intensive Care*. (2018) 6:6. doi: 10.1186/s40560-018-0277-9

42. Korula PJ, Nayyar V, Stachowski E, Karuppusami R, Peter JV. An observational study on the practice of noninvasive ventilation at a tertiary level Australian intensive care unit. *Aust Crit Care*. (2020) 33:89–96. doi: 10.1016/j.aucc.2018.11.067

43. Chen Q, Liu M, Liu B, Li W, Gao D, Xie L, et al. Predictive factors for failure of noninvasive ventilation in adult intensive care unit: a retrospective clinical study. *Can Respir J*. (2020) 2020:1324348–7. doi: 10.1155/2020/1324348

44. Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. *BMC Pulm Med*. (2014) 14:19. doi: 10.1186/1471-2466-14-19

45. Ghazala L, Hatipoğlu U, Devnani T, Covert E, Hanks J, Edwards K, et al. Duration of noninvasive ventilation is not a predictor of clinical outcomes in patients with acute exacerbation of COPD and respiratory failure. *Can J Respir Ther*. (2021) 57:113–8. doi: 10.29390/cjrt-2021-021

46. Liengswangwong W, Yuksen C, Thepkong T, Nakasint P, Jenpanitpong C. Early detection of non-invasive ventilation failure among acute respiratory failure patients in the emergency department. *BMC Emerg Med*. (2020) 20:80. doi: 10.1186/s12873-020-00376-1

47. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med*. (2017) 195:67–77. doi: 10.1164/rccm.201606-1306OC

48. Bai L, Ding F, Xiong W, Shu W, Jiang L, Liu Y, et al. Early assessment of the efficacy of noninvasive ventilation tested by HACOR score to avoid delayed intubation in patients with moderate to severe ARDS. *Ther Adv Respir Dis*. (2022) 16:17534666221081042. doi: 10.1177/17534666221081042

49. Bima P, Pivetta E, Baricocchi D, Giamello JD, Risi F, Vesan M, et al. Lung ultrasound improves outcome prediction over clinical judgment in COVID-19 patients evaluated in the emergency department. *J Clin Med*. (2022) 11:3032. doi: 10.3390/jcm11113032

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 05 December 2023
DOI 10.3389/fmed.2023.1252586

OPEN ACCESS

EDITED BY
Zhongheng Zhang,
Sir Run Run Shaw Hospital, China

REVIEWED BY
Marianna Laviola,
University of Nottingham, United Kingdom
Savvas Lampridis,
Hammersmith Hospital, United Kingdom

*CORRESPONDENCE
Chaoyang Li
licylicy111@163.com
Jie Zhang
462378103@qq.com

RECEIVED 04 July 2023
ACCEPTED 01 November 2023
PUBLISHED 05 December 2023

CITATION
Lin C, Wang D, Yan Y, Zhong R, Li C and Zhang J (2023) Transnasal humidified rapid-insufflation ventilator exchange compared with laryngeal mask airway for endoscopic thoracic sympathectomy: a randomized controlled trial. *Front. Med.* 10:1252586. doi: 10.3389/fmed.2023.1252586

Transnasal humidified rapid-insufflation ventilator exchange compared with laryngeal mask airway for endoscopic thoracic sympathectomy: a randomized controlled trial

Chunmei Lin, Dandan Wang, Yulu Yan, Ruihan Zhong, Chaoyang Li* and Jie Zhang*

Department of Anesthesiology, Huazhong University of Science and Technology Union Shenzhen Hospital, Shenzhen, China

Background: Transnasal humidified rapid-insufflation ventilator exchange (THRIVE) has the characteristics of operating easily and maintaining oxygenation and eliminating CO_2, which makes it possible to be used in endoscopic thoracic sympathectomy (ETS). The application of THRIVE in ETS remains undefined. The purpose of this randomized controlled study is to assess the efficacy between THRIVE and laryngeal mask airway (LMA) for ETS.

Methods: In total, 34 patients from May 2022 to May 2023 in Huazhong University of Science and Technology Union Shenzhen Hospital undergoing ETS were randomly divided into a THRIVE group ($n = 17$) and an LMA group ($n = 17$). A serial arterial blood gas analysis was conducted during the perioperative period. The primary outcome was the arterial partial pressure of carbon dioxide ($PaCO_2$) during the perioperative period. The secondary outcome was arterial partial pressure of oxygen (PaO_2) during the perioperative period.

Results: The mean (SD) highest $PaCO_2$ in the THRIVE group and LMA group were 99.0 (9.0) mmHg and 51.7 (5.2) mmHg, respectively ($p < 0.001$). The median (interquartile range) time to $PaCO_2 \geq 60$ mmHg in the THRIVE group was 26.0 min (23.2–28.8). The mean (SD) PaO_2 was 268.8 (89.0) mmHg in the THRIVE group and 209.8 (55.8) mmHg in the LMA group during surgery ($p = 0.027$).

Conclusion: CO_2 accumulation in the THRIVE group was higher than that of the LMA group during ETS, but THRIVE exhibited greater oxygenation capability compared to LMA. We preliminarily testified that THRIVE would be a feasible non-intubated ventilation technique during ETS under monitoring $PaCO_2$.

KEYWORDS

transnasal humidified rapid-insufflation ventilator exchange, laryngeal mask airway, endoscopic thoracic sympathectomy, carbon dioxide accumulation, apneic oxygenation

1 Introduction

Hyperhidrosis (HH) is a major dermatologic disease characteristic of producing excessive sweat, occurring in 0.6–1% of the general public and resulting in a negative effect on the patient's life (1). The best treatment for patients with primary HH is endoscopic thoracic sympathectomy (ETS), especially for the HH of palmar manifestations (2). Endotracheal intubation has been performed to offer patients adequate oxygen during ETS. Hsieh et al. (3) compared 17 patients receiving anesthesia with double-lumen endobronchial tube ventilation and 19 patients receiving anesthesia with laryngeal mask airway (LMA) during ETS for palmar HH, and they found there was no difference in oxygen saturation between the two groups during operation, which makes it possible for LMA to be used in ETS. There are many complications with the use of endotracheal intubation and LMA. Takahata et al. (4) have found a number of problems and complications with airway management by endotracheal intubation and laryngeal mask airway, including hoarseness and arytenoids dislocation by using endotracheal intubation and aspiration, oropharyngeal leak and gastric distension by using LMA. In addition, Bhavani-Shankar et al. (5) described negative pressure injury occurring with the use of LMA during the resection of a ganglion cyst.

Transnasal humidified rapid-insufflation ventilator exchange (THRIVE), a new type of non-intubated ventilation, provides patients with continuous oxygen through a non-invasive high-flow nasal cannula. Compared with traditional apneic oxygenation, carbon dioxide (CO_2) removal of THRIVE is regulated by the mutual effect of supraglottic flow vortices and flow oscillation created by cardiogenic oscillation (6). The first application of THRIVE was in neonates for the treatment of apnea and the prevention of extubation failure (7). In addition, it is generally considered that THRIVE can be used in intensive care units and the induction of anesthesia to supply oxygen therapy for patients (8, 9). Moreover, several groups have successfully applied THRIVE in patients with microlaryngoscopic surgery (10, 11). In a recent prospective study, we have indicated that THRIVE can be an effective and safe ventilation way for 19 Chinese patients performing microlaryngoscopic surgery (12). Furthermore, Liu et al. (13) have used THRIVE for oxygenation in thoracoscopic segmentectomy and exhibited that it can maintain oxygen reserves during surgery. ETS has the characteristics of short operation time and good treatment effect for primary HH. At present, the main airway management methods in ETS are tracheal intubation (including single-lumen tube and double-lumen tube) and laryngeal mask airway. These airway management methods have damage to the trachea. As a non-tracheal intubation mode of ventilation, THRIVE has no damage to the airways. However, THRIVE can cause carbon dioxide accumulation after prolonged use. We have found that the $PaCO_2$ increased by 1.68 ± 0.12 mmHg every minute linearly in non-laser microlaryngoscopic surgery (12). Moreover, thoracoscopic surgery may involve the absorption of CO_2 into blood, which increases the risk of hypercapnia. Therefore, whether THRIVE can be safely and reliably applied to ETS requires further research.

In this study, we performed a randomized controlled study to evaluate the efficacy between THRIVE and LMA for ETS and tried to provide more evidence about the application of THRIVE in ETS for the Chinese population.

2 Materials and methods

2.1 Methods

This study was conducted from May 2022 to May 2023 in Huazhong University of Science and Technology Union Shenzhen Hospital. It was approved by the Chinese Clinical Trial Registry (ChiCTR2200061446). The written consent of all participants was required before performing the experiment.

2.2 Study object

After meeting the inclusion criteria, 34 patients were recruited and randomized into the THRIVE group ($n = 17$) and the LMA group ($n = 17$; Figure 1). In total, 34 patients presenting for both sides of uniportal EST were recruited. Patients were randomly assigned to the THRIVE group and LMA group in a 1:1 ratio. Investigators (YY) conducted the block randomization by using a computer and placed the identifier in opaque sealed envelopes. After patients arrived in the operating room with a sealed envelope, the anesthesiologist (JZ or CLin) opened the envelopes and performed the assigned intervention. The inclusion criteria were as follows: primary HH, elective surgery within 1 h, aged 18–60 years, American Society of Anesthesiologists (ASA) physical status 1–2. The exclusion criteria were as follows: the body mass index (BMI) of $\geq 30\ kg \cdot m^{-2}$, a Mallampati grade of 3–4, and the patient with extensive pleural adhesion or pleural hypertrophy or thoracic surgery history.

2.3 Study protocol

All patients were monitored for the following indicators before and during surgery, including electrocardiogram, invasive blood pressure, saturation of peripheral oxygen (SpO_2), bispectral index (BIS), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), and potential of hydrogen (pH). In the THRIVE group, the THRIVE was applied to offer patients oxygen with a concentration of 95% at 50 L/min before the administration of anesthetics (Figure not shown). In the LMA group, pre-oxygenation was conducted with a mask at a 5 L/min flow of 100% oxygen. All participants were induced by using propofol, sufentanil, and vecuronium until a BIS value of less than 60. A laryngeal mask airway was established in the LMA group after pre-oxygenation for 3–5 min (Figure not shown). The tidal volume was set at 6–7 mL/kg and the respiratory rate was set at 12–15 breaths/min. In both groups, the maintenance of anesthesia with propofol and remifentanil depended on the BIS value and surgical procedure. Propofol and remifentanil were administered in the target-controlled infusion of the Marsh model. In addition, it is necessary to use parecoxib sodium, tramadol, palonosetron, and dexamethasone as general anesthetic adjuvant drugs. At the beginning of the operation, 1% ropivacaine was used for local anesthesia at the incision. After an incision was made in the fourth intercostal space, the endoscope was inserted into the pleural cavity; thus, we could observe the thoracic sympathetic nerve (Figure not shown). In the THRIVE group, we immediately performed mask ventilation when the SpO_2 of patients dropped below 95% or the $PaCO_2$ accumulated more than 110 mmHg during the procedure. In

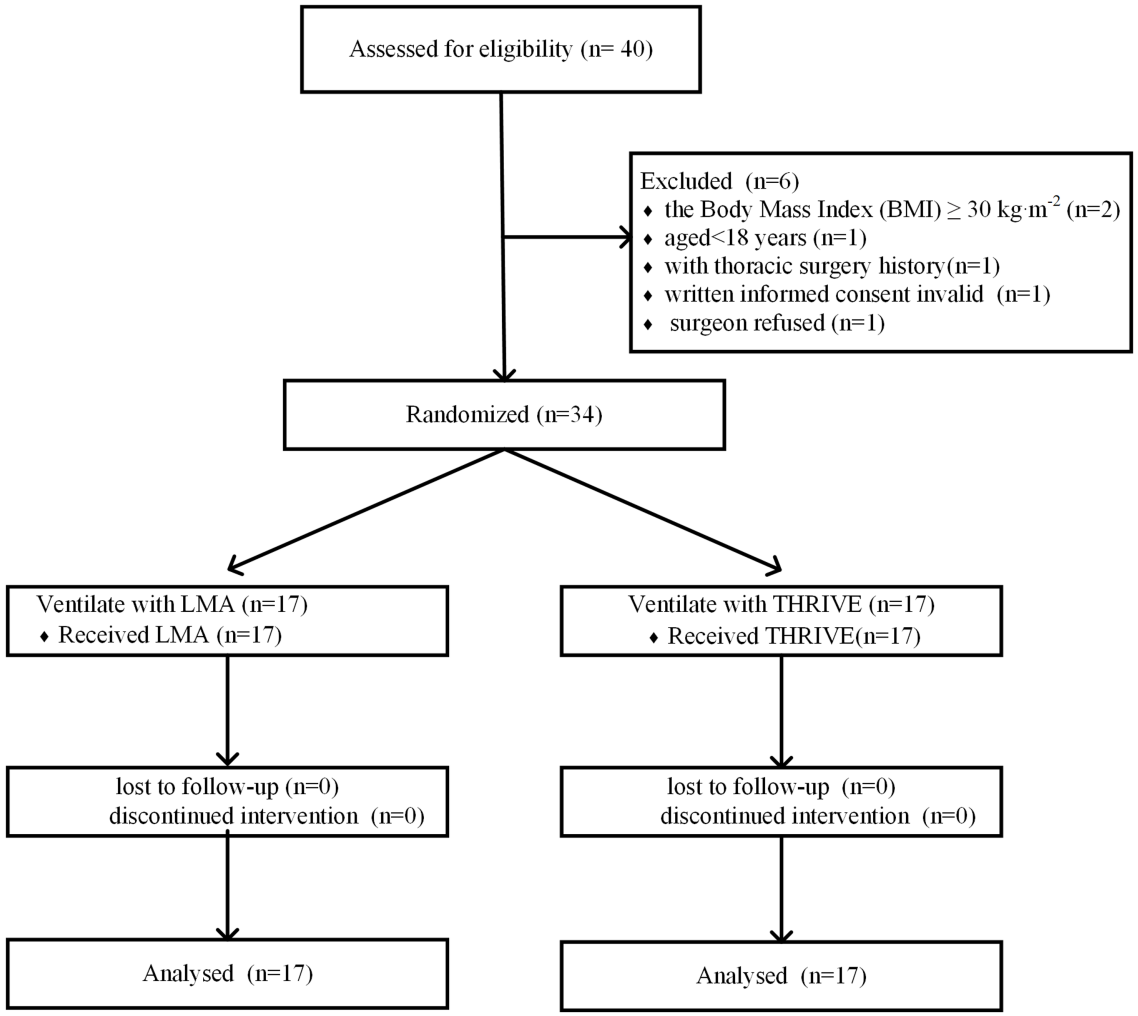


FIGURE 1
Consolidated standards of reporting trials flow diagram. THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; LMA, Laryngeal mask airway.

addition, the elimination of CO_2 to less than 60 mmHg was carried out by using mask ventilation after the surgery. Meanwhile, THRIVE was discontinued when the consciousness of the patient was regained, and then the patient was transferred to the post-anesthesia care unit (PACU). In the LMA group, the laryngeal mask airway was removed after the recovery of the patient's consciousness, and then the participant was transported to PACU.

2.4 Data collection and analyses

The primary outcome was the measurement of $PaCO_2$ during the perioperative period. Secondary outcomes were (1) the measurements of PaO_2 and pH at seven test points, respectively; (2) time to $PaCO_2 \geq 60$ mmHg; (3) the number of intraoperative ventilations by mask; (4) the number of pharyngalgia after operation. The seven time points were defined as follows: before pre-oxygenation (T_0), after an induction (T_1), at the beginning of operation (T_2), at the end of sympathetic nerve excision on one side (T_3), at the end of sympathetic nerve excision on the other side (T_4), at the end of the operation (T_5), and the moment of consciousness recovery (T_6). Data analysis was performed by using SPSS25.0. The use of mean standard deviation toward continuous data and the application of number (%) to categorical data was conducted in our study. The *t*-test was applied for continuous variables and a value of $p < 0.05$ was identified as statistically significant. Time to $PaCO_2 \geq 60$ mmHg was conducted by Kaplan–Meier curves and compared between the THRIVE group and the LMA group by the log-rank statistic. Median time to $PaCO_2 \geq 60$ mmHg and 95% confidence intervals (CIs) are shown.

3 Results

No differences were observed in the patient characteristics between the groups (Table 1). No differences were observed in $PaCO_2$, PaO_2, and SPO_2 before pre-oxygenation (Table 2). As shown in Table 3, the mean (SD) highest $PaCO_2$ in the THRIVE group was 99.0 (9.0) mmHg, while the mean highest $PaCO_2$ was 51.7 (5.2) mmHg in the LMA group, and the difference was statistically significant ($p < 0.001$). The mean (SD) lowest PaO_2 during surgery in the THRIVE

TABLE 1 Patients and intraoperative characteristics.

	THRIVE ($n = 17$)		LMA ($n = 17$)		p
Age, years	26.6	8.7	23.6	4.6	0.219
Weight, kg	57.4	9.8	58.0	10.5	0.854
BMI, kg/m^2	21.1	2.3	21.3	3.2	0.84
Female, *n* (%)	10 (59)		10 (59)		1
ASA, *n* (%)	10 (59)		9 (53)		0.739
I	10		9		
II	7		8		
Surgery duration, min	18.4	8.8	19.9	6.6	0.571

Values are mean ± standard deviation or *n* (%); BMI, Body mass index; ASA, American society of anesthesiologists; *n* (%), number (0%); THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; and LMA, Laryngeal mask airway.

TABLE 2 Baseline arterial blood gas data and oxygen saturation.

	THRIVE ($n = 17$)		LMA ($n = 17$)		p
$PaCO_2$ in room air, mmHg	37.7	3.6	38.6	5.0	0.561
PaO_2 in room air, mmHg	96.4	6.5	100.3	10.5	0.198
SpO_2 in room air, %	98.5	1.6	98.6	1.0	0.930

Values are mean ± standard deviation; $PaCO_2$, Arterial partial pressure of carbon dioxide; PaO_2, Arterial partial pressure of oxygen, SpO_2, Saturation of peripheral oxygen; THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; LMA, Laryngeal mask airway.

TABLE 3 Study outcomes.

	THRIVE ($n = 17$)		LMA ($n = 17$)		p
Highest $PaCO_2$ during operation, mmHg	99.0	9.0	51.7	5.2	0.000
Lowest PaO_2 during operation, mmHg	268.8	89.0	209.8	55.8	0.027
Lowest SpO_2 during operation, %	99.1	1.4	99.6	0.8	0.139
Number of intraoperative mask ventilation, *n* (%)	3 (20)		0 (0)		0.073
Number of pharyngalgia after operation, *n* (%)	0 (0)		2 (12)		0.154

Values are mean ± standard deviation or *n* (%). $PaCO_2$, Arterial partial pressure of carbon dioxide; SpO_2, Saturation of peripheral oxygen; PaO_2, Arterial partial pressure of oxygen; THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; LMA, Laryngeal mask airway.

group was 268.8 mmHg (89.0 mmHg), while that of the LMA group was 209.8 mmHg (55.8 mmHg), and the difference was statistically significant ($p = 0.027$). There was no difference in the lowest SpO_2 during surgery between groups. During the surgery, three patients among 17 participants were performed mask ventilation in the THRIVE group, while none of the patients in the LMA group required intraoperative mask ventilation. In addition, after the operation, two patients in the LMA group had pharyngalgia, while none had pharyngalgia in the THRIVE group.

The tendency of $PaCO_2$ during the perioperative period is presented in Figure 2A. $PaCO_2$ in the THRIVE group increased by 56.5 mmHg from T_0 to T_5 and dropped below 60 mmHg at T6. $PaCO_2$ in the LMA group showed no significant change during the perioperative period. A statistically relevant difference in $PaCO_2$ was observed between the two groups during operation ($p < 0.01$). As shown in Figure 2B, pH in the THRIVE group decreased from T_0 to T_5 and rose to approximately 7.3 at T_6. There was no significant fluctuation in the pH of LMA patients, and a statistically relevant difference was observed between the two groups during surgery ($p < 0.01$). As shown in Figure 2C, the PaO_2 of both groups increased significantly after pre-oxygenation. Moreover, PaO_2 of the THRIVE group achieved higher levels compared to the LMA group during operation, and a significant difference was observed between the two groups at T_3 and T_5 ($p < 0.01$).

As shown in Figure 3, the Median (inter-quartile range) time to $PaCO_2 \geq 60$ mmHg in the THRIVE group was 26.0 min (23.2–28.8). The risk of $PaCO_2 \geq 60$ mmHg was significantly higher in the THRIVE group than in the LMA group (hazard ratio = 41.67; 95% CI 10.31–166.7; Log-rank $p < 0.01$).

4 Discussion

Transnasal humidified rapid-insufflation ventilator exchange can remove CO_2 through by the mutual effect of supraglottic flow vortices and flow oscillation created by cardiogenic oscillation (6). Recent studies (9, 14) have proved the lower accumulation rates of CO_2 with THRIVE compared with historical (15), which has implied that THRIVE can produce the clearance of CO_2. However, the CO_2 created by anesthetic techniques in historical studies and the analysis method of recent studies have made the results contentious. In our study, we have found that the mean highest concentration of THRIVE group was 99.0 mmHg. This verified that the major limiting factor of using THRIVE in ETS is hypercarbia. According to the

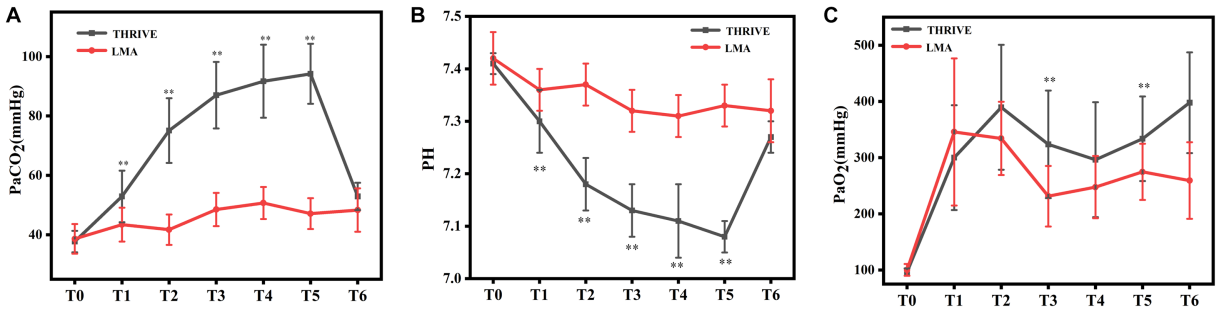
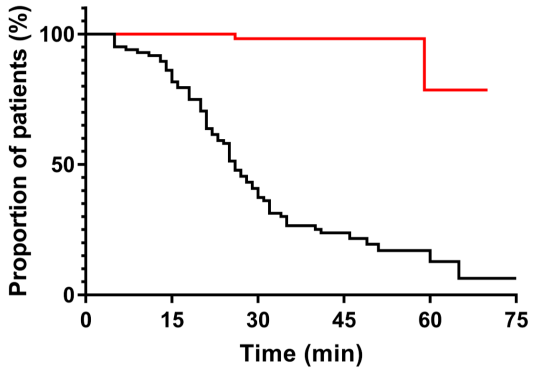


FIGURE 2
Arterial blood gas analysis. $PaCO_2$ **(A)**, pH **(B)**, and PaO_2 **(C)** in seven test points between THRIVE and LMA groups during the perioperative period. T_0: before pre-oxygenation, T_1: after an induction, T_2: at the beginning of the operation, T_3: at the end of sympathetic nerve excision on one side, T_4: at the end of sympathetic nerve excision on the other side, T_5: at the end of the operation, and T_6: the moment of consciousness recovery. THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; LMA, Laryngeal mask airway; $PaCO_2$, Arterial partial pressure of carbon dioxide; pH, The potential of hydrogen; and PaO_2, Arterial partial pressure of oxygen. $^{**}p < 0.01$ vs. LMA group.



Number at risk

THRIVE	0	11	15	2	1	0
LMA	0	0	0	0	1	0

FIGURE 3
Kaplan–Meier curves of time to $PaCO_2 \geq 60$ mmHg in the THRIVE group (black line) and LMA group (red line). The hazard ratio comparing between THRIVE and LMA groups was 41.67 (95% confidence interval, 10.31–166.7; Log-rank $p < 0.01$). THRIVE, Transnasal humidified rapid-insufflation ventilator exchange; LMA, Laryngeal mask airway.

Henderson–Hasselbalch equation, the degree to which respiratory acidosis affects the body is significantly associated with hypercapnia. Although CO_2 drops quickly postoperatively, the serious consequence of short-term respiratory acidosis requires vigilance, especially for gerontic patients with cardiovascular disease. During the perioperative period, severe hypercapnia can result in clinical adverse events (16–18). Kerr et al. (16) reported an unusual case of hypercapnia and surgical emphysema during transanal endoscopic microsurgery, which led to delayed postoperative ventilatory failure. A study done by Son et al. (17) found that intraoperative hypercarbia may be related to a high incidence of postoperative nausea and vomiting (PONV). In addition, Kim et al. (18) indicated that the circulatory response to hypercapnia is an increase in arterial pressure and heart rate. Therefore, the application of THRIVE in ETS should be limited to young patients without serious cardiovascular and cerebrovascular diseases. It is beneficial to use a transcutaneous CO_2 monitor during operation.

The duration of apnea will extend with THRIVE by eliminating CO_2, but several studies have indicated that CO_2 will accumulate as the use of THRIVE prolongs (12, 19). Booth et al. (19) have shown that CO_2 accumulation in the apnea group was double than that of the spontaneous ventilation group after 30 min with the application of THRIVE. In addition, Ma et al. (12) have found that CO_2 increased to 112 mmHg when the apnea time extended to 65 min. The level of $PaCO_2$ less than 60 mmHg has been reported without serious adverse reaction (12). In our study, we found that the median time to $PaCO_2 \geq 60$ mmHg in the THRIVE group was 26.0 min. Moreover, thoracoscopic surgery may involve the absorption of CO_2 into blood, which increases the risk of hypercapnia. Therefore, the duration of operation should be strictly controlled to avoid severe hypercapnia. Hypoxia is more likely to occur in obese patients due to decreased functional residual capacity and lung compliance as well as increased oxygen consumption and respiratory work. Additionally, 10% of obese patients have difficulty with mask ventilation because of anatomic factors. Although Wu et al. (20) have indicated that PaO_2 achieved a higher level with the use of THRIVE in obese patients, one study showed that high BMI patients were prone to hypoxemia (21). Therefore, only patients with a BMI less than 30 were included in our study to ensure safety.

HH is a disease that can negatively affect patients' quality of life, and some studies have shown that the best treatment for patients with primary HH is endoscopic thoracic sympathectomy. The main airway management methods in ETS are tracheal intubation (including single-lumen tube and double-lumen tube) and laryngeal mask airway. There is currently no research on the application of THRIVE to ETS. LMA has been used in thoracic surgery due to its good oxygenation capability and convenient airway management (5); however, the adverse effects created by LMA are not trivial. THRIVE can deliver humidified air to the patients at 37°C and 100% humidity through nasal ducts. Several studies have verified that THRIVE can prevent the reduction of intraoperative temperature and maintain oxygen reserve during thoracoscopic surgery for patients with early lung cancer (22, 23). This is the first study to evaluate the effect of THRIVE and LMA for ETS. Compared to LMA, THRIVE can lead to

a higher CO_2 accumulation but has greater oxygenation capability during ETS. Our study preliminarily testified that THRIVE can be availably utilized in ETS under CO_2 monitoring.

As shown in Figure 2, $PaCO_2$ increased from 37.7 mmHg at T_0 to 94.2 mmHg at T_5 in the THRIVE group, while $PaCO_2$ did not change significantly in the LAM group. These results indicate that we should be alert to the occurrence of hypercapnia when applying THRIVE for ETS. $PaCO_2$ should be closely monitored with the use of THRIVE, and if necessary, mask ventilation should be used to promote the emission of carbon dioxide. Additionally, $PaCO_2$ in the THRIVE group decreased rapidly to below 60 mmHg after the surgery, indicating that THRIVE can be safely used in ETS for young patients with BML < 30 Kg/m^2. The contraction and relaxation of the lungs can affect the exposure of the surgical field with the application of LMA during ETS, and the anesthesiologist may be required to temporarily suspend artificial ventilation of the patient to minimize the impact of lung movement on the surgical exposure. However, this problem does not exist when choosing THRIVE. In our study, we found that two out of 17 patients in the LAM group experienced postoperative pharyngalgia, which may be caused by a laryngeal mask to the pharyngeal tissue. This adverse reaction will affect postoperative patient comfort. However, no postoperative pharyngalgia was observed in the THRIVE group.

Transnasal humidified rapid-insufflation ventilator exchange can transport a high concentration of oxygen by combining a high fraction and high flow of inspired oxygen and produce positive pharyngeal pressure to enhance oxygenation (24). Several studies have reported that THRIVE can effectively prevent the happen of arterial desaturation (21, 25). In our study, the PaO_2 of both groups increased significantly after pre-oxygenation, and the PaO_2 of the THRIVE group achieved higher levels compared to the LMA group during operation, which proved the powerful ability of THRIVE to improve oxygenation. Our study showed that SpO_2 of THRIVE group was greater than 95% during the perioperative period (data not shown). However, Vourc'h et al. (26) manifested that THRIVE promoted the occurrence of desaturation below 95% by generating a lower concentration of end-tidal oxygen. These discrepancies might be due to the differences in the measurement of desaturation and the oxygenation protocol. In addition, the progressive decrease of PaO_2 during operation and the gradual rise of PaO_2 with the end of surgery were observed in our study. Intrapulmonary shunt and pulmonary atelectasis may be the possible reason, which is a common phenomenon with the administration of anesthetics (24). The delivery of high oxygen concentration by THRIVE may also result in atelectasis (27). Moreover, artificial pneumothorax caused by surgery can lead to atelectasis and PaO_2 reduction.

We should pay more attention to the following limitations of our study. First, only 34 patients were enrolled in our study, and it is important to include more data to verify the feasibility of THRIVE in ETS. Second, there is no double blindness between the anesthesiologist and the data analyst, which may affect the objectivity of the results. Third, the mean age of the patients included in our study was young adults and BMI was less than 30 kg/m^2, and the availability of THRIVE in ETS for older patients with BMI greater than 30 kg/m^2 remains uncertain. Fourth, the feeling of the surgeon during the operation (mainly refers to the impact of breathing on the exposure of the surgical field) will be an important factor in evaluating the effectiveness of using THRIVE, which should be noticed in future. Finally, real-time monitoring of exhaled CO_2 could not be done increasing the risk to patients. Moreover, the applicability of findings to other case scenario may be different.

5 Conclusion

We have conducted a randomized controlled study that THRIVE would be an effective and safe non-intubated ventilation technique during ETS under monitoring $PaCO_2$. Although THRIVE exhibited significantly greater CO_2 accumulation compared to LMA during operation, THRIVE presented better apneic oxygenation capability than LMA. These findings indicate that THRIVE may be regarded as an alternative anesthetized technique for young and BMI less than 30 Kg/m^2 patients undergoing ETS. Further studies are needed to evaluate the efficacy of THRIVE for older patients with a BMI greater than 30 Kg/m^2. This will help to determine the appropriate population for THRIVE during ETS and improve clinical safety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Chinese Clinical Trial Registry. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CLin, DW, and JZ: study design. CLin, DW, YY, and RZ: information collection. CLin and DW: analysis of data. CLin: manuscript drafting. CLin, DW, YY, RZ, CLi, and JZ: manuscript revision, editing, and approval. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors would like to express our thanks to all participants in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Adar R, Kurchin A, Zweig A, Mozes M. Palmar hyperhidrosis and its surgical treatment: a report of 100 cases. *Ann Surg*. (1977) 186:34–41. doi: 10.1097/00000658-197707000-00006

2. Cerfolio RJ, De Campos JR, Bryant AS, Connery CP, Miller DL, Decamp MM, et al. The society of thoracic surgeons expert consensus for the surgical treatment of hyperhidrosis. *Ann Thorac Surg*. (2011) 91:1642–8. doi: 10.1016/j.athoracsur.2011.01.105

3. Hsieh YJ, Chen CM, Lin HY, Young TF. Experience of anesthesia during transthoracic endoscopic sympathectomy for palmar hyperhidrosis: comparison between double-lumen endobronchial tube ventilation and laryngeal mask ventilation. *Acta Anaesthesiol Sin*. (1994) 32:13–20.

4. Takahata O, Iwasaki H. Problems and complications in airway management by endotracheal intubation and laryngeal mask airway. *Anaesthesia*. (2006) 25:517–22. doi: 10.1007/s002610000084

5. Bhavani-Shankar K, Hart NS, Mushlin PS. Negative pressure induced airway and pulmonary injury. *Canad Anaesth Soc J*. (1997) 44:78–81. doi: 10.1007/bf03014328

6. Hermez LA, Spence CJ, Payton MJ, Nouraei SAR, Patel A, Barnes TH. A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (THRIVE). *Anaesthesia*. (2019) 74:441–9. doi: 10.1053/j.jvca.2016.07.003

7. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support in preterm infants: a review of the evidence. *Neonatology*. (2012) 102:300–8. doi: 10.1002/14651858.CD006405

8. Mir F, Patel A, Iqbal R, Cecconi M, Nouraei SA. A randomized controlled trial comparing transnasal humidified rapid insufflation ventilator exchange (THRIVE) pre-oxygenation with facemask pre-oxygenation in patients undergoing rapid sequence induction of anaesthesia. *Anaesthesia*. (2017) 72:439–43. doi: 10.12659/MSM.938168

9. Patel A, Nouraei SA. Transnasal humidifed rapid-insufation ventilatory exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia*. (2015) 70:323–9. doi: 10.1111/anae.12923

10. Benninger MS, Zhang ES, Chen B, Tierney WS, Bryson PC. Utility of transnasal humidified rapid insufflation ventilatory exchange for microlaryngeal surgery. *Laryngoscope*. (2021) 131:587–91. doi: 10.1002/lary.28776

11. Nekhendzy V, Saxena A, Mittal B, Sun E, Sung K, Dewan K, et al. The safety and efficacy of transnasal humidified rapid-insufflation ventilatory exchange for Laryngologic surgery. *Laryngoscope*. (2020) 130:E874–81. doi: 10.1002/lary.28562

12. Ma B, Liu F, Wang D, Zhong R, Lin K, Li S, et al. High-flow nasal cannula in nonlaser microlaryngoscopic surgery: a prospective study of 19 cases in a Chinese population. *BMC Anesthesiol*. (2022) 22:81. doi: 10.1186/s12871-022-01627-3

13. Liu HY, Chiang XH, Hung MH, Wang ML, Chen JS. Nonintubated uniportal thoracoscopic segmentectomy for lung cancer. *J Formos Med Assoc*. (2020) 119:1396–404. doi: 10.1016/j.jfma.2020.03.021

14. Gustafsson IM, Lodenius A, Tunelli J, Ullman J, Fagerlund MJ. Apnoeic oxygenation in adults under general anaesthesia using Transnasal humidified rapid-insufflation Ventilatory exchange (THRIVE)—a physiological study. *Brit J Anaesth*. (2017) 118:610–7. doi: 10.1093/bja/aex036

15. Toner AJ, Douglas SG, Bailey MA, Avis HJ, Pillai AV, Phillips M, et al. Effect of apneic oxygenation on tracheal oxygen levels, tracheal pressure, and carbon dioxide accumulation: a randomized, controlled trial of buccal oxygen administration. *Anesth Analg*. (2019) 128:1154–9. doi: 10.1213/ANE.0000000000003810

16. Kerr K, Mills GH. Intra-operative and post-operative hypercapnia leading to delayed respiratory failure associated with transanal endoscopic microsurgery under general anaesthesia. *Brit J Anaesth*. (2001) 86:586–9. doi: 10.1093/bja/86.4.586

17. Son JS, Oh JY, Ko S. Effects of hypercapnia on postoperative nausea and vomiting after laparoscopic surgery: a double-blind randomized controlled study. *Surg Endosc*. (2017) 31:4576–82. doi: 10.1007/s00464-017-5519-8

18. Kim MC, Yi JW, Lee BJ, Kang JM. Influence of hypercapnia on cardiovascular responses to tracheal intubation. *J Crit Care*. (2009) 24:627.e1–5. doi: 10.1016/j.jcrc.2009.01.012

19. Booth AWG, Vidhani K, Lee PK, Coman SH, Pelecanos AM, Dimeski G, et al. The effect of high-flow nasal oxygen on carbon dioxide accumulation in apneic or spontaneously breathing adults during airway surgery: a randomized-controlled trial. *Anesth Analg*. (2020) 133:133–41. doi: 10.1213/ANE.0000000000005002

20. Wu YM, Li CC, Huang SY, Su YH, Wang CW, Chen JT, et al. A comparison of oxygenation efficacy between high-flow nasal cannulas and standard facemasks during elective tracheal intubation for patients with obesity: a randomized controlled trial. *J Clin Med*. (2022) 11:1700. doi: 10.3390/jcm11061700

21. Schutzer-Weissmann J, Wojcikiewicz T, Karmali A, Lukosiute A, Sun R, Kanji R, et al. Apnoeic oxygenation in morbid obesity: a randomised controlled trial comparing facemask and high-flow nasal oxygen delivery. *Br J Anaesth*. (2022) 130:103–10. doi: 10.1016/j.bja.2021.12.011

22. Lai CJ, Yeh KC, Wang ML, Tai WH, Cheng YJ. Heated humidified high-flow nasal oxygen prevents intraoperative body temperature decrease in non-intubated thoracoscopy. *J Anesth*. (2018) 32:872–9. doi: 10.1007/s00540-018-2567-8

23. Wang ML, Hung MH, Chen JS, Hsu HH, Cheng YJ. Nasal high-flow oxygen therapy improves arterial oxygenation during one-lung ventilation in non-intubated thoracoscopic surgery. *Eur J Cardiothorac Surg*. (2018) 53:1001–6. doi: 10.1093/ejcts/ezx450

24. Lumb AB, Thomas CR. High-flow nasal therapy—modelling the mechanism. *Anaesthesia*. (2019) 74:420–3. doi: 10.1111/anae.14544

25. Wong DT, Dallaire A, Singh KP, Madhusudan P, Jackson T, Singh M, et al. High-flow nasal oxygen improves safe apnea time in morbidly obese patients undergoing general anesthesia: a randomized controlled trial. *Anesth Analg*. (2019) 129:1130–6. doi: 10.1213/ANE.0000000000003966

26. Vourc'h M, Baud G, Feuillet F, Blanchard C, Mirallie E, Guitton C, et al. High-flow nasal cannulae versus non-invasive ventilation for preoxygenation of obese patients: the PREOPTIPOP randomized trial. *EClinicalMedicine*. (2019) 13:112–9. doi: 10.1016/j.eclinm.2019.05.014

27. Lumb AB. Just a little oxygen to breathe as you go off to sleep. Is it always a good idea? *Brit J Anaesth*. (2007) 99:769–71. doi: 10.1093/bja/aem329

Frontiers in Medicine

Translating medical research and innovation into improved patient care

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact