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RESEARCH ARTICLE

The significance of ventilator-associated pneumonia in SARS-CoV-2 patients: a systematic review

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ABSTRACT

Aim: We performed a systematic review to compare the prevalence and mortality burden of ventilator-associated pneumonia (VAP) in SARS-CoV-2 patients.

Material and Methods: We conduct this systematic review and meta-analysis according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. We searched PubMed, Scopus, Web of Science, Embase, and Cochrane from the database's inception to February 10, 2021.

Results: Five studies were identified. VAP occurred in 45.2% in the COVID-19 group compared to 26.0% for the non-COVID-19 group (OR = 3.17; 95% CI [1.94, 5.18]; $p < 0.001$; $I2 = 67\%$). Three studies showed VAP recurrence to be 41.6% in the COVID-19 group and 20.2% in the non-COVID-19 group (OR = 3.12; 95% CI [1.87, 5.22]; $p < 0.001$; $I2 = 0\%$). The mortality rate in COVID-19 vs. non-COVID-19 varies, amounting to 32.1% and 26.3%, respectively (OR = 1.33; 95% CI [1.07, 1.66]; $p = 0.010$; $I2 = 49\%$).

Conclusions: The findings from this case series reveal that the presence of ventilator-associated pneumonia in SARS-CoV-2 patients is a source of significant mortality. This study strengthens the importance of non-invasive mechanical ventilation strategies and also highlights the need for careful infection control surveillance in invasive mechanical ventilation. Due to the high rates of VAP and associated increased mortality, uprating antibiotic/antifungal therapy selection is also paramount in caring for SARS-CoV-2 cases admitted to the ICU.

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In the early months of the pandemic, the role of secondary bacterial infections in hospitalized SARS-CoV-2 patients was not well understood (Cox et al., 2020; Dzieciatkowski et al., 2020; Szarpak et al., 2021). Early reports from Wuhan hospitals indicated a high rate of secondary bacterial infections and increased mortality in intubated SARS-CoV-2 patients (Zhou et al., 2020). However, alternative research reported that cases of superimposed bacterial infections in patients with SARS-CoV-2 are exceptionally lower than other respiratory viral infections such as influenza and recommended that patients should not be given antibiotics indiscriminately (Langford, 2020). While concerns of antibiotic overuse and subsequent development of antibiotic resistance held merit, the rates of bacterial infections in critically ill SARS-CoV-2 patients being exceptionally high is now overwhelmingly clear (Langford et al., 2020; Maes et al., 2021). As more research has emerged, ventilator-associated pneumonia (VAP) has clearly become the most common and important bacterial infection in critically ill SARS-CoV-2 patients (Maes et al., 2021; Vincent et al., 2020; Wu et al., 2020).

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With up to 80% of ICU admissions requiring invasive mechanical ventilation and a particularly high prevalence of acute respiratory distress syndrome (ARDS), SARS-CoV-2 patients are particularly susceptible to contracting VAP, which is associated with increased mortality and cost (Argenziano et al., 2020; Nair & Niederman, 2014). Emerging data show the increased risk of VAP associated with SARS-CoV-2 to have exceeded anticipated rates due to changes in the pulmonary microbiome or prolonged duration of mechanical ventilation in critically ill patients (Maes et al., 2021).

Highlighting the proportion of SARS-CoV-2 patients who are at high risk of contracting VAP is critical to mitigating and improving clinical outcomes during the current pandemic. Acknowledging this secondary infection control problem will also lead to better VAP prevention strategies, improved patient outcomes, and augmented pandemic countermeasures.

We performed a systematic review to compare the prevalence and mortality burden of VAP in SARS-CoV-2 patients. In doing so, we hope to highlight how additional VAP surveillance, prevention, and treatment regimens could help improve clinical outcomes during a pandemic.

Methods

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to examine the prevalence and mortality rate of VAP in SARS-CoV-2 patients (Moher et al., 2015). The PRISMA methodology has been selected as the ideal methodology for synthesizing knowledge in a timely fashion so that findings can positively impact clinical care. Our analysis included only studies where SARS-CoV-2 and non-SARS-CoV-2 patients were examined using the same VAP diagnostic criteria and methods. In each case, VAP is defined as the pneumonia that develops following at least a 48-hour period of intubation without evidence of previous infection. We included randomized controlled trials with more than 30 patients and excluded reviews, editorials, and letters. Due to COVID-19 and the need to present clinically relevant results as soon as possible, the study has not been registered in the international registry of systematic reviews. Ethical committee approval does not apply to this study.

Search Strategy

The literature search was screened by two reviewers (M.P. and L.S.) independently using electronic databases (i.e., PubMed, Scopus, Web of Science, Embase, and Cochrane) from database inception to February 10, 2021. The search used the following terms: “ventilator-associated pneumonia” OR “VAP” OR “respiratory infection” OR “hospital acquired pneumonia” OR “respiratory tract” OR “nosocomial pneumonia” AND “SARS-CoV-2” OR “COVID-19.” All full-text studies meeting the inclusion criteria were reviewed by both reviewers for final inclusion. We also evaluated the reference lists of the relevant clinical trials to identify additional studies for potential inclusion. The retrieved bibliographic records were downloaded and imported with duplicates removed in the Endnotes.

Inclusion

Studies included in this case series fall under the following criteria (PICOS): Must have (1) participants, patients with cardiac arrest due to any causes under 18 years old; (2) intervention, COVID-19 patients; (3) comparison, non-COVID-19 patients; (4) outcomes, detailed information for survival; and (5) study design, randomized controlled trials, quasi-randomized or observational studies comparing TTM and standard care for their effects in patients with cardiac arrest.

Exclusion Criteria

Studies as reviews, animal studies, case reports, letters, conference/poster abstracts, or articles not containing original data were excluded.

Data Extraction

For each included study, data extraction was performed independently by two reviewers (L.S. and M.P.) using a standard form. Disagreements were resolved by consulting with a third reviewer (A.G.). The following variables on study characteristics have been extracted: primary author, year of publication, country, study period, study design, patients’ age, sex, BMI, identification of VAP, the incidence of VAP, length of ICU stay, duration of mechanical ventilation (MV), 28-day mortality, ICU mortality, VAP, and recurrence of VAP. Studies potentially describing overlapping data are considered.

Outcome Measures

The primary outcome measured was mortality during hospitalization. Secondary outcomes were mortality at ICU, length of stay, and VAP prevalence.

Evaluating the Quality of the Papers

The Cochrane Collaboration's tool (ROBINS-I) for assessing the risk of bias was used (Sterne et al., 2016). The items assessed were confounding; selection of participants; classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; and selection of the reported results. Robvis application was used to for visualize risk-of-bias assessments (McGuinness & Higgins, 2020). The review authors' judgments about each risk-of-bias item are provided in Figures S1-S2.

Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan Ver. 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration). Case series analysis was performed whenever the outcome measures of two or more studies are available. For dichotomous outcomes, we applied the Mantel–Haenszel method, and pooled results are presented as risk ratios (RR) with 95% confidence interval (CI). When a study reports the continuous outcome as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. (2005). For continuous outcome measures, the inverse variance weighted random-effects model was used to estimate the pooled difference in the outcome measure for fixation-versus-no fixation with a corresponding 95% CI. Heterogeneity was assessed statistically using I^2 (no heterogeneity, $I^2 = 0–25\%$; moderate heterogeneity, $I^2 = 25–50\%$; large heterogeneity, $I^2 = 50–75\%$; and extreme heterogeneity, $I^2 = 75–100\%$) (Safiejko et al., 2020). The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. A $p < 0.05$ was taken to indicate statistical significance. Statistical testing was two-tailed. A $p < 0.05$ was considered statistically significant for the two-tailed testing.

Assessment of Bias

A formal assessment for risk of bias was conducted. The funnel-plot and Egger's regression test were used to assess publication bias (Higgins et al., 2011).

Results

Study Characteristics and Methodological Quality Assessment

We identified a total of 471 potentially relevant studies (Figure 1). After removing duplicates, 107 studies were screened with 15 undergoing a full-text review. After the review, 10 studies were excluded from the analysis due to unusable results and incomparable data. We included 5 studies in the final assessment (Hue et al., 2020; Luyt et al., 2020; Maes et al., 2021; Razazi et al., 2020; Rouzé et al., 2021).

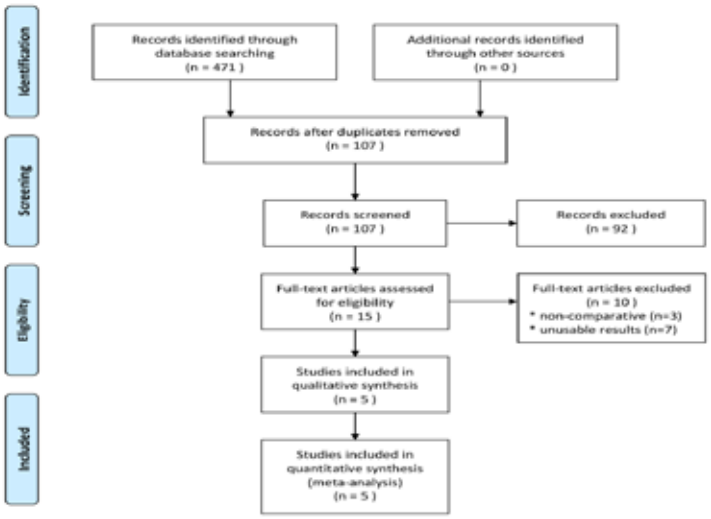

Figure 1. Case series flow chart of included and excluded studies.

The studies included for the case series include 1,616 patients. A summary of the risk of bias in the included studies as agreed by the authors is presented in supplementary Figures S1 and S2.

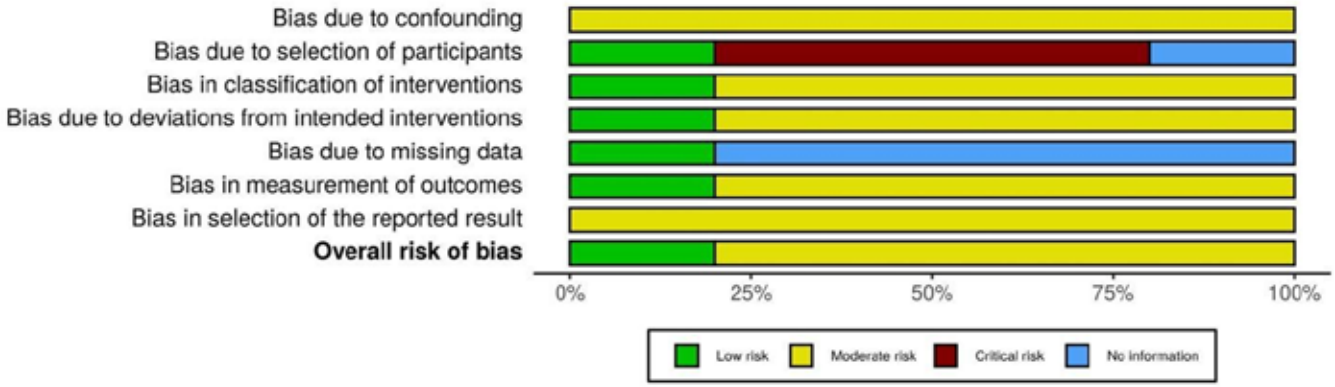

Figure S1. Evaluating bias in all included studies across the various domains. Green, red, and yellow circles respectively indicate low, high, and unclear risk of bias.

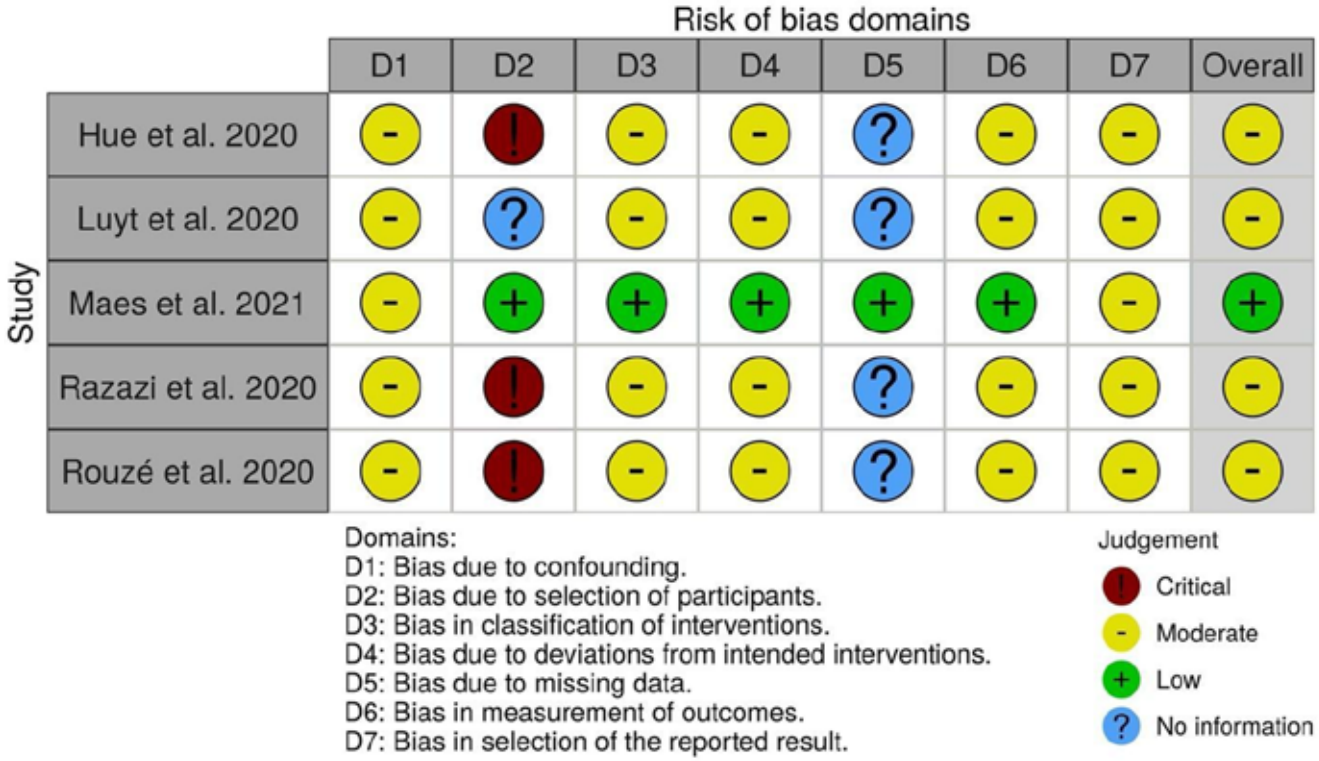

Figure S2. Summary of the risk of bias among the included studies.

Although some of the domains in the included studies had indeterminate or high risk of bias, the aggregate risk of bias for all the studies was low.

Outcomes

The analysis shows VAP to have occurred in all five studies, at a rate of 45.2% in the COVID-19 group compared to 26.0% for the non-COVID-19 group (*OR* = 3.17; 95% CI [1.94, 5.18]; $p < 0.001$; $I^2 = 67\%$; Figure 2). Three studies show a VAP recurrence of 41.6% in the COVID-19 group and 20.2% in the non-COVID-19 group (*OR* = 3.12; 95% CI [1.87, 5.22]; $p < 0.001$; $I^2 = 0\%$; Figure 3).

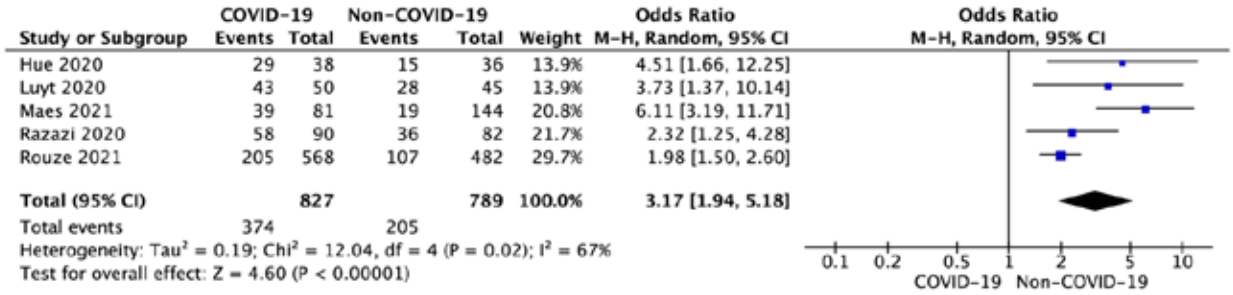

Figure 2. Forest plot of VAP occurrence in the COVID-19 group versus the non-COVID-19 group.[1]

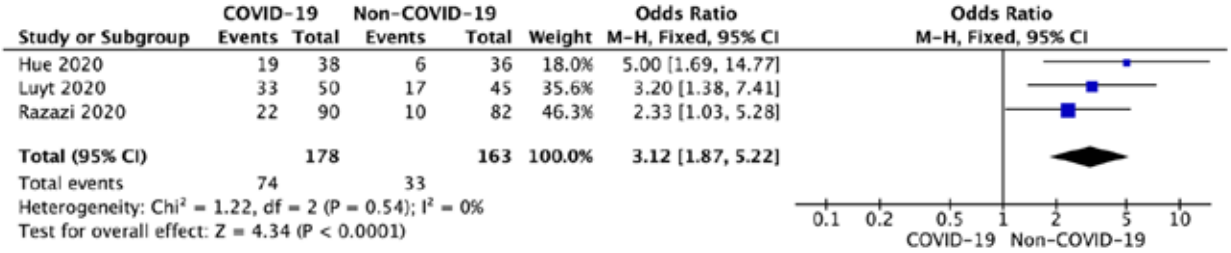

Figure 3. Forest plot of VAP recurrence in the COVID-19 versus non-COVID-19 groups.[7]

Five trials reported an ICU mortality rate in COVID-19 versus non-COVID-19 patients to vary, amounting to 32.1% and 26.3%, respectively (*OR* = 1.33; 95% CI [1.07, 1.66]; $p = 0.010$; $I^2 = 49\%$; Figure 4). Moreover, three studies reported 28-day mortality rates of 31.3% for COVID-19 patients compared to 26.8% for non-COVID-19 patients (*OR* = 1.63; 95% CI [0.87, 3.02]; $p = 0.12$; $I^2 = 65\%$; Figure 5).

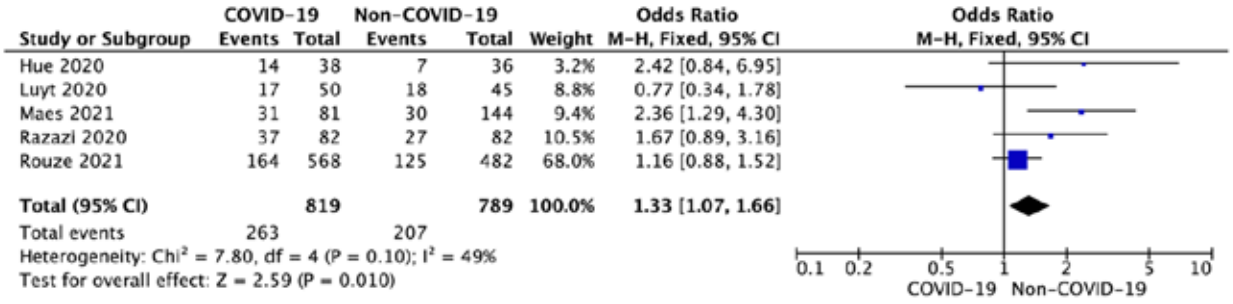

Figure 4. Forest plot of ICU mortality in COVID-19 versus non-COVID-19 group.[7]

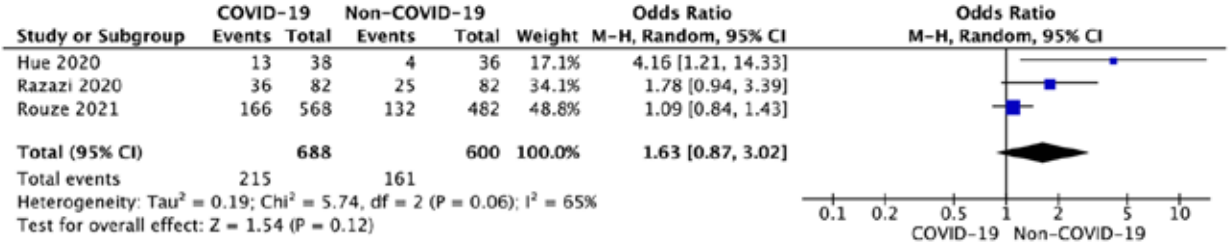

Figure 5. Forest plot of 28-days mortality in COVID-19 versus non-COVID-19 group.[7]

1 The center of each square represents the weighted mean difference for individual trials, and the corresponding horizontal line represents the 95% confidence interval. The diamonds represent pooled results. Procedure time is presented in seconds.

Discussion

To our knowledge, this is the first case-series and systematic review examining the increased occurrence, recurrence, and mortality rate of VAP in SARS-CoV-2 patients.

This analysis abundantly clarifies that VAP is a serious issue for critically ill patients with SARS-CoV-2 and the healthcare systems that care for them. As the VAP rates in ventilated SARS-CoV-2 patients are significantly higher than those in other patients, these nosocomial infections are undoubtedly contributing to hospital capacity, staffing, and supply-chain issues. In this regard, the results from this study support the continued strategy of avoiding early intubation and utilizing non-invasive mechanical ventilation methods to support patients, a practice which has played a role in helping countless patients avoid complications and survive hospitalization.

In many countries including the United States where strict VAP surveillance and reporting is insufficient or nosocomial infections are ignored, these infections are likely to have particularly dire impacts. VAP is a well-studied problem with multiple randomized control studies and endorsed preventative strategies, but adherence to VAP prevention protocols can vary widely. International scientific societies such as the CDC and Spanish Society of Intensive & Critical Care Medicine have created and recommended strategies for preventing and combating VAP; however, too little attention has been paid to strengthening these initiatives during the pandemic (Álvarez-Lerma et al., 2018). Instead, the medical community continues to struggle with identifying preventative and therapeutic strategies to directly address SARS-CoV-2, an approach that has been met with uneven results.

Over time, the pandemic will continue to force patients to undergo invasive mechanical ventilation with the placement of an endotracheal tube or tracheostomy tube. Invariably, the use of these airway devices, while medically necessary, will lead to increased cases of VAP, time in the ICU, time on mechanical ventilation, and patient mortality. One conclusion that can be extrapolated from this study highlights the role of VAP in critically ill SARS-CoV-2 to be important, as improvements in VAP prevention and surveillance will lead to improvements in outcomes for SARS-CoV-2 patients.

National efforts to further improve VAP prevention and surveillance, such as the 2018 Pneumonia Zero Program undertaken by 181 Spanish ICUs, have been proven effective at reducing the rate of VAP and are likely to contribute to improved ICU outcomes during the pandemic. Recommendations from the Pneumonia Zero Program include appropriate airway management, hand hygiene, cuff pressure control, chlorhexidine mouth washing, semi-recumbent positioning, sedation holidays, short systemic antibiotic therapy during intubation, and continuous subglottic secretion drainage (Álvarez-Lerma et al., 2018).

VAP prevention protocols such as careful cuff pressure control (Nseir et al., 2011; Wen et al., 2019), elevated head-of-the-bed position (Alexiou et al., 2009), oral hygiene with chlorhexidine (Ji et al., 2020; Satheeshkumar et al., 2020), and hand hygiene are well studied, effective, and for the most part non-modifiable. Improvements in mechanical ventilation, antibiotic therapy, subglottic secretion drainage (Lacherade et al., 2010; Muscedere et al., 2011), and timing of tracheostomy (Araujo de Franca et al., 2021; Wang et al., 2019) are key areas where improvements and innovation can have a marked impact on the outcome of the current pandemic. Of note, significant improvements to the current protocols will likely be in the form of changes in airway devices design, as VAP is caused by the microaspiration of pathogenic fluid from the upper airways into the lower airways along the body of the airway device.

Strategies to mitigate microaspiration are an area of significant research and innovation. In the past, modifying the balloon of endotracheal and tracheostomy tubes in terms of material compliance and shape were thought to mitigate this problem. However, recent research looking at improvements in balloon material and shape has demonstrated no improvement in the incidence of hospital-acquired pneumonia including VAP (Araujo de Franca et al., 2021; Wang et al., 2019). Meanwhile, subglottic secretion drainage continues to show promising benefits, with multiple studies and innovations showing reductions in VAP incidence. Recognizing these facts, a number of companies (e.g., Venner PneuX, Tracoe Medical GmbH, and Nevap) have introduced more effective multiport subglottic secretion drainage devices for mitigating VAP. Further research into these devices in critically ill SARS-CoV-2 patients are needed in order to quantify the benefit of these new devices and their role in VAP prevention.

This study has several limitations. VAP diagnosis in patients with an underlying viral infection and ARDS is challenging. Surveillance and diagnostic criteria for VAP vary widely around the world, and invasive mechanical ventilation is utilized differently among different populations. However, adopting strategies and practices that better mitigate VAP will improve clinical outcomes for SARS-CoV-2 patients.

Conclusion

The findings from this case series analysis reveal the presence of ventilator-associated pneumonia in SARS-CoV-2 patients to be a significant source of mortality. This study strengthens the importance of non-invasive mechanical ventilation strategies and also highlights the need for careful infection control surveillance in invasive mechanical ventilation. Due to the high rates of VAP and associated increased mortality, uprating antibiotic/antifungal therapy selection is also paramount in caring for SARS-CoV-2 cases admitted to the ICU.

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