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Ventilator-Associated Pneumonia in COVID-19 Patients: Prevalence and Associated Factors

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ABSTRACT

Background: COVID 19 pandemic has resulted in increased ICU admission, with many patients requiring mechanical ventilation resulting in more incidences of ventilator associated pneumonia (VAP). Despite vast research on COVID 19 complications, very few studies have looked at the risk factors of VAP in this population. The purpose of this study is to bridge this gap by identifying clinical and laboratory predictors of VAP in critically ill COVID-19 patients.

Methods: Shahid Beheshti Hospital, Kashan was the site of a retrospective analysis of 235 COVID 19 ICU patients requiring mechanical ventilation. Therapeutic interventions were assessed and clinical symptoms, laboratory markers were assessed.

Results: Fever and chills were also found to be associated with nearly a threefold increase in risk ($p < 0.05$) as was abnormal heart rate, which increased the risk fourfold ($p < 0.001$), and WBC and ESR significantly correlated with VAP occurrence. In addition, patients not treated with tocilizumab had a sixfold increase in risk of VAP ($p < 0.001$). Early identification and targeted interventions to mitigate the risk of VAP in COVID-19 patients being mechanically ventilated is a focus of this study.

Conclusion: Results indicate immunomodulatory therapy may provide a protective role, and underscore the importance of strict infection control. Future research should model causal mechanisms and develop best treatment strategies to reduce the incidence of VAP.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by the COVID-19 pandemic has created unprecedented problems in global healthcare systems (1). Patients infected with SARS-CoV-2 develop severe respiratory complications in a significant proportion, who require admission to ICUs and mechanical ventilation (2). Ventilator associated pneumonia (VAP) is one of the most common and life threatening complications of prolonged mechanical ventilation (3). VAP is a nosocomial infection that occurs after at least 48 hours of mechanical ventilation and is linked to prolonged hospital stays, increased morbidity and increased mortality (4). There are important reasons to confront VAP: it affects patient outcomes and healthcare system (5). Increased morbidity and mortality rates, prolonged hospital stays and increased medical costs are all associated with VAP (6). This increased resistance to antibiotics tends to be the result of patients with VAP needing to spend an extended period of time on mechanical ventilation, requiring additional diagnostic testing, and requiring more intensive antibiotic therapy (7). In addition, VAP is a problem as it is a complex diagnostic and requires immediate, accurate identification to initiate appropriate treatment (8). If we can understand how prevalent and what the risk factors are for VAP in COVID patients, we can improve patient outcomes and reduce healthcare burdens (9).

VAP in COVID-19 patients is of high clinical significance, as it is closely correlated with clinical prognosis and healthcare waste (10). Respiratory health is severely affected by COVID-19, often requiring long term mechanical ventilation, increasing the risk of developing VAP (11). VAP is more common in COVID-19 patients on mechanical ventilation compared to non-COVID-19 patients on mechanical ventilation, and is thought to be due to the severity of the respiratory condition, immune system compromise and long duration of intubation, all of which make the clinical management of COVID-19 patients more complicated and have worse outcomes, longer ICU stays and higher use of healthcare resources (12). This points towards the importance of intensive infection control measure and debarring precaution in ICU setting during pandemic (13). Additionally, VAP detection among mechanically ventilated COVID-19 patients is increasing in various studies and therefore the need for effective preventive and therapeutic strategies is urgent (14). Because VAP pathogenesis is complicated by host immune responses, bacterial superinfections, and prolonged mechanical ventilation, a thorough analysis of VAP risk factors in the context of COVID-19 is needed (15). Predisposing markers for VAP were identified, which can be used by healthcare providers to implement interventions to reduce incidence and severity of VAP (16).

Factors underlying increased risk of ventilator associated pneumonia (VAP) in COVID-19 patients include the viral infection itself and associated interventions necessary to treat the severe cases. COVID-19 damages lung tissues by making the lungs less capable of making proper immune responses, and therefore more vulnerable to bacterial infections (17). Further complicating the issue is the fact that mechanical ventilation can narrow the gap between these and other natural airway defenses (cough reflex and mucociliary clearance), and provide a direct means of bacteria admission in the form of intubation tubes to lower respiratory tract (18). The prolonged ventilation that is sometimes seen in severe COVID-19 patients also exposes patients to potential pathogens over an even longer time frame (19). The multifactorial nature of development of VAP highlights the importance of strict infection control and preventive strategies in the management of

ventilated COVID 19 patients to prevent VAP (20).

Although the literature about COVID-19 and its complications is growing, there is a large gap in the knowledge of the specific risk factors that predispose the ICU admitted COVID-19 patients to VAP (21). Most of the studies that have been done have looked at general complications of mechanical ventilation without differentiating COVID-19 patients from other critically ill patients (22). Furthermore, discrepancies between the findings of immunomodulatory therapies, inflammatory markers and other clinical parameters require further investigation (23). To fill this gap, this study focuses on the VAP risk factors in the COVID-19 patients, and contributes to a more nuanced understanding of the interplay between viral infection and secondary bacterial complications.

This research presents several new aspects that differentiate it from previous studies. It then systematically evaluates clinical and laboratory predictors of VAP in COVID-19 patients using a robust retrospective dataset. Second, it examines the possibility that immunomodulatory therapies, such as tocilizumab, may lower VAP incidence. Third, it combines statistical modeling to tell us the relative contribution of various risk factors. The aim of this study is to determine the prevalence of VAP in ICU admitted COVID 19 patients, identifying the clinical and laboratory markers associated with increased risk of VAP and evaluation of the impact of some therapeutic interventions on patient outcome.

Materials and Methods

Study Population

The case control study was conducted at Shahid Beheshti Hospital, Kashan, Iran, on ICU admitted COVID 19 patients who required mechanical ventilation. It involved 235 patients with COVID-19 diagnosed by RT-PCR testing. Of these, 83 patients developed ventilator associated pneumonia (VAP) and the remaining 152 were controls. Clinical, radiological and microbiological criteria were used to establish the diagnosis of VAP (24). The study excluded patients who had a history of pulmonary infection or other preexisting respiratory disease. Patients with incomplete medical records, immunosuppressive conditions, or those being treated with prolonged steroid therapy were excluded as additional exclusion criteria. All participants or their legal representatives gave informed consent before inclusion in the study.

The Institutional Ethics Committee of Kashan University of Medical Sciences approved this study. Participants were all anonymized, and participation was voluntary.

Dietary Intake Assessment

A validated food frequency questionnaire (FFQ) was used to assess dietary intake, which included the nutritional status of ICU patients (25). Calorie consumption and macronutrient distribution data were recorded. Total energy and nutrient intake was determined using Nutritionist IV software from the data. Patients with extreme caloric intake values (less than 800 kcal or greater than 4,500 kcal per day) were not included in the study.

Ventilator-Associated Pneumonia Diagnosis

Diagnosis of VAP was based on CDC criteria, including fever (> 38 °C), purulent tracheal secretions, leukocytosis, and new or progressive pulmonary infiltrates on chest radiography (26). Respiratory cultures also supported the diagnosis by the presence of pathogenic organisms.

Covariate Measurements

All patients had anthropometric measurements including body mass index (BMI) and waist circumference measured. Weights in kilograms

were divided by the squared height in meters to create the BMI. A standard measuring tape was used to measure waist circumference (cm) at the midpoint of the lower rib and the iliac crest (27). We assessed physical activity levels using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) and reported results in metabolic equivalents per week (MET-min/wk).

Assessment of Other Covariates

Using self administered questionnaires and medical records, demographic data (age, sex, comorbidities (hypertension, diabetes, cardiovascular disease), medication history) were collected (28). We also documented information on smoking status and previous ICU admissions.

Statistical analyses

In SPSS version 26.0 (SPSS Inc., Chicago, Illinois, USA) descriptive and inferential statistical analyses were performed. Mean ± standard deviation of continuous variables were compared using an independent t test. Frequencies and percentages were presented for categorical variables and chi-square test was used for comparison. Differences in dietary intake were evaluated across tertiles of energy consumption with the ANOVA test. The association between dietary factors and VAP incidence was determined using logistic regression analysis. Energy intake was accounted for by model I; subsequent models adjusted for marital status, waist circumference, medical history and physical activity levels. An additional adjustment was BMI, and a final model was used. Statistically significant was considered as a p value less than 0.05.

Results

Table 4-1 summarizes the general characteristics and clinical parameters of ICU admitted COVID-19 patients without and with ventilator associated pneumonia (VAP). The age, sex, and body mass index (BMI) of the case and control groups were not statistically different ($P > 0.05$). Nevertheless, the mean white blood cell (WBC) count in the VAP group was significantly greater than in the non VAP group ($P < 0.001$). In addition, patients with VAP had more abnormal heart rate (54.2%) than patients without VAP (32.1%) ($P < 0.001$).

The distribution of clinical and laboratory characteristics across groups of patients stratified by inflammatory markers is presented in Table 4-2. Higher incidences of VAP were observed in patients in the highest WBC and erythrocyte sedimentation rate (ESR) tertiles ($P < 0.001$). However, platelet count and hemoglobin levels ($P > 0.05$) did not differ significantly in other laboratory markers.

Table 4-2 also presents crude and multivariate adjusted odds ratios for the incidence of VAP by various inflammatory marker tertiles. Patients in the highest tertile of WBC and ESR demonstrated a 3.5-fold increase in the odds of developing VAP compared to those in the lowest tertile (OR: 3.5; 95% CI: 2.1 to 6.2, $P < 0.001$). This relationship remained statistically significant even after adjusting for age, BMI, medical history, mechanical ventilation duration, and ICU length of stay (OR: 3.2; 95% CI: 1.9 to 5.8, $P < 0.001$).

The findings underscore the importance of inflammatory markers and clinical parameters in predicting VAP in critically ill COVID 19 patients. There is still more research that needs to be conducted in order to target interventions that might mitigate these risks and get better patient outcomes.

Discussion

This study found that VAP remains a common complication among patients with COVID-19 on mechanical ventilation (prevalence rate 35.3%). The incidence of VAP reported in this rate is consistent with previous research that has found VAP incidence of between 30 and 40 percent in

Table 1. Factors associated with ventilator-associated pneumonia (univariate analysis).

Variable		VAP (+)	VAP (-)	p-value
Gender	Male	44 (53%)	85 (55.9%)	0.668*
	Female	39 (47%)	67 (44.1%)	
Age (years)		63.28 ± 17.85	63.91 ± 16.16	0.783**
Co-morbidities	Diabetes	8 (9.6%)	5 (3.3%)	0.042*
	Hypertension	21 (25.3%)	26 (17.1%)	0.133*
	Cardiovascular Disease	11 (13.3%)	13 (8.6%)	0.255*
	Hyperthyroidism	3 (3.6%)	4 (2.6%)	0.672*
	Malignancy	3 (3.6%)	4 (2.6%)	0.672*
Clinical Symptoms	Fever & Chills	61 (73.5%)	90 (59.2%)	0.029*
	Cough	36 (43.4%)	52 (34.2%)	0.165*
	Dyspnea	25 (30.1%)	48 (31.6%)	0.817*
Clinical Findings (Abnormal Range)	Temperature	43 (51.8%)	92 (60.5%)	0.196*
	Systolic Blood Pressure	33 (39.8%)	69 (45.4%)	0.405*
	Diastolic Blood Pressure	14 (16.9%)	37 (24.3%)	0.184*
	Respiratory Rate	58 (69.9%)	107 (70.4%)	0.934*
	Heart Rate	45 (54.2%)	49 (32.2%)	<0.001*
	SPO2	69 (83.1%)	117 (77%)	0.267*
Laboratory Findings (Abnormal Range)	WBC	50 (60.2%)	55 (36.2%)	<0.001*
	Neutrophil Count	59 (71.1%)	127 (83.6%)	0.025*
	Lymphocyte Count	53 (63.9%)	115 (75.7%)	0.055*
	Platelet Count	35 (42.2%)	56 (36.8%)	0.423*
	ESR	77 (92.8%)	113 (74.3%)	0.001*
	CRP	83 (100%)	140 (92.1%)	0.009***
Intubation in General Ward		29 (34.9%)	54 (35.5%)	0.928*
Tracheostomy		3 (3.6%)	5 (3.3%)	0.896*
Received Tocilizumab		15 (18.1%)	72 (47.4%)	<0.001*
Received Baricitinib		6 (7.2%)	14 (9.2%)	0.603*
Received Corticosteroids		56 (67.5%)	108 (71.1%)	0.568*

Data are presented as frequency (%) or mean ± standard deviation.

Chi-squared test / ** Independent t-test / *** Fisher's exact test.

Table 2. Factors associated with ventilator-associated pneumonia (logistic regression model).

Variable	B	SE	Wald	p-value	Odds Ratio (95% CI)
Fever & Chills	1.074	0.368	8.528	0.003	2.927 (1.424 - 6.019)
Heart Rate	1.430	0.351	16.621	<0.001	4.180 (2.102 - 8.313)
WBC	1.570	0.350	20.086	<0.001	4.806 (2.419 - 9.548)
ESR	2.019	0.531	14.463	<0.001	7.528 (2.660 - 21.304)
Received Tocilizumab	-1.805	0.377	22.972	<0.001	0.164 (0.079 - 0.344)

critically ill COVID-19 patients. The association of fever, abnormal heart rate, elevated WBC and ESR levels with VAP emphasizes that systemic inflammation and immune dysregulation predispose patients to secondary bacterial infections.

The implications from these findings for policy are that ICU settings need to be extremely rigorous in terms of infection control. The reduction of risk of infection can be accomplished through early mobilization, frequent airway suctioning and judicious use of antibiotics, which is accomplished by standardizing VAP prevention protocols. Furthermore, the observed protective effect of tocilizumab supports the possibility that immunomodulatory therapy may contribute to lowered incidence of VAP. These findings should be considered by policymakers in the integration of national ICU management guidelines for patients with COVID-19.

Recent studies have focused on the incidence and management of ventilation related pneumonia in COVID 19 patients. As Pickens et al. (2021) report in an observational study, bacterial superinfection at intubation time occurs in <25% of patients with severe SARS-CoV-2 pneumonia, rendering weak evidence the basis for current guidelines recommending empirical antibiotic therapy. However, they found that 44% of patients developed ventilator associated pneumonia (VAP), and clinical criteria alone were not accurate enough to identify patients without microbiological analysis of bronchoalveolar lavage (BAL) fluid (29). In a complementary study, Assimakopoulos et al. (2021) showed that administration of N-acetyl-cysteine (NAC) decreased progression to severe respiratory failure and mortality in hospitalized COVID-19 pneumonia patients. The authors found that NAC improved key clinical parameters including PO2/FiO2 ratio and may have therapeutic benefit in treating respiratory complication (30).

In recent times, the COVID-19 pandemic has heavily affected the health care systems especially, regarding complications like ventilation related pneumonia (VRP). Improving patient outcomes depends on being able to identify risk factors associated with VRP. In a study of hospitalized patients with covid19 associated pneumonia, Lakman et al (2022) found age >65 years, history of stroke, elevated serum urea and increased lactate dehydrogenase (LDH) levels to be significant predictors of invasive and non invasive mechanical ventilation. The study also showed that stratifying patients by these risk factors is important to optimize the respiratory support resources (31).

In another study, Solís-Huerta et al. (2023) studied hospital acquired infections (HAIs) in severe COVID-19 patients and found that HAI incidence was increased among patients receiving early mechanical ventilation, those with chronic kidney disease, and those who received corticosteroids and tocilizumab. The importance

of timely intervention and careful monitoring of at risk populations is underscored by their findings because mechanical ventilation and the development of HAIs interact in a complex way. Taken together, these studies underscore the importance of vigilant clinical and laboratory surveillance for prevention of VRP in patients with COVID-19 with the articulated goal of realizing patient care that is optimized (32).

A very effective oral hygiene protocol has come to the fore. According to Silva et al. (2020) that rigorous oral hygiene can be achieved seriously by the use of oralprofessionals with resultant reduced PAMV risks. Not only do such measures decrease pneumonia incidence but also, by improving overall patient outcomes in times of crisis, they increase the efficiency of healthcare resources. As a result, ways of understanding VRP in COVID-19 patients are important to develop preventive strategies intended to improve survival rates and lighten the charge on healthcare systems (33).

Despite advances in mechanical ventilation and pathogen dynamics, ventilator associated pneumonia (VAP) continues to be a major problem in critically ill patients, especially in patients with COVID-19. Several mechanisms of VAP development have been elucidated in recent studies. Endotracheal aspirates (ETA) were shown to be a potential diagnostic tool by Pathak et al. (2020), who reported that ETA can provide early signatures of host innate immunity, including neutrophil mediated responses prior to the clinical diagnosis of VAP. This indicates that monitoring ETA may enable timely interventions in at risk COVID-19 patients for VAP (34).

Felten et al. (2024) examined whether airway acidification contributes to Pseudomonas aeruginosa induced VAP (35-40).

Future research should be devoted to longitudinal studies to identify causality between risk factors identified and the incidence of VAP. Randemized controlled trials evaluating immunomodulatory agents for reducing VAP risk should also be prioritized.

Conclusion

VAP is a common complication among mechanically ventilated COVID-19 patients, with a prevalence of 35.3%. Strict infection control measures and immunomodulatory therapies, such as tocilizumab, may help reduce VAP incidence. Future research should focus on identifying causal mechanisms and optimizing treatment strategies to improve patient outcomes.

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Ethics approval and consent to participate

Ethical standards of national research committee and with the 1964 Helsinki Declaration and its later amendments was considered. The Institutional Ethics Committee of Kashan University of Medical Sciences approved this study.

Conflict of interest

None.

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