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ORIGINAL RESEARCH

Determinants, microbial profile, and clinical outcomes of late-onset ventilator-associated pneumonia in mechanically ventilated patients: A matched case-control study

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ABSTRACT

Background: Late-onset ventilator-associated pneumonia (LVAP) is a major healthcare-associated infection contributing to significant morbidity, mortality, and healthcare costs in intensive care units (ICUs). LVAP, occurring 96 hours or more after intubation, is frequently associated with multidrug-resistant (MDR) pathogens. This study aimed to identify the determinants of LVAP, the microbial profile, and the impact on clinical outcomes among mechanically ventilated patients in a tertiary care hospital.**Material and Methods:** A 1:1 matched case-control study was conducted over 12 months in the ICU of SukhSagar Medical College, Jabalpur. A total of 280 patients (140 cases with LVAP and 140 controls without LVAP) were included. Cases were defined as patients who developed pneumonia 96 hours or more after intubation. Controls were matched based on APACHE II score and duration of mechanical ventilation. Data on demographics, clinical history, risk factors, microbiological findings, and outcomes were collected and analyzed using appropriate statistical tests.**Results:** Key risk factors for LVAP included prior use of steroids/immunosuppressants (18.6% vs. 2.1%; $p = 0.003$), re-intubation (16.4% vs. 3.6%; $p = 0.018$), and bacteremia (27.1% vs. 5.0%; $p = 0.001$). Patients with LVAP had a longer median duration of mechanical ventilation (16.5 vs. 11.0 days; $p< 0.001$) and ICU stay (21.0 vs. 16.0 days; $p = 0.046$). Mortality was significantly higher in LVAP cases (27.1% vs. 14.3%; $p = 0.022$). The most common pathogens were *Acinetobacter* spp. (49.3%) and *Pseudomonas* spp. (41.4%), with 59.3% of cases involving MDR organisms.**Conclusions:** LVAP is associated with significant risk factors, predominantly MDR Gram-negative bacteria, and worse clinical outcomes. Effective preventive strategies, early diagnosis, and targeted antibiotic therapy are critical to improving patient outcomes and reducing the burden of LVAP in ICUs.

Key words: Ventilator-Associated Pneumonia (VAP), Multidrug-Resistant (MDR) Pathogens, Mechanical Ventilation, Intensive Care Unit (ICU)

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is a significant healthcare-associated infection, contributing to morbidity, mortality, prolonged intensive care unit (ICU) stay, and increased healthcare costs among mechanically ventilated patients[1]. Defined as pneumonia occurring 48 hours or more after endotracheal intubation and mechanical ventilation, VAP remains a major concern in critical care settings[1]. The incidence of VAP varies widely, with rates in India reported to range from 9% to 24%. Globally, mortality attributed to VAP ranges from

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24% to 50%, with rates as high as 76% in cases caused by multidrug-resistant (MDR) organisms[2].

VAP is classified into two categories based on the time of onset: *early-onset VAP (EVAP), occurring within 96 hours of intubation, and late-onset VAP (LVAP), developing after 96 hours*[2]. EVAP is typically associated with community-acquired organisms and tends to have a better prognosis. In contrast, LVAP is often linked to MDR pathogens, such as *Acinetobacter* spp., *Pseudomonas* spp., and *Klebsiella pneumoniae*, resulting in higher morbidity and mortality[2]. The emergence of drug-resistant bacteria in LVAP, particularly MDR *Pseudomonas* and *Acinetobacter*, further complicates treatment and adversely impacts clinical outcomes[3]. Several factors contribute to the development of VAP, including prolonged mechanical ventilation, re-intubation, use of steroids or immunosuppressants, bacteremia, and underlying comorbidities such as chronic obstructive pulmonary disease (COPD) and diabetes mellitus[4]. Early identification of these determinants is crucial for effective VAP prevention and management. By examining the risk factors, microbial profile, and outcomes associated with LVAP, this research will provide insights into effective strategies for prevention, early diagnosis, and management of LVAP, ultimately improving patient care in critical care units.

OBJECTIVES

i) To identify the risk factors associated with the development of late-onset ventilator-associated pneumonia (LVAP) in mechanically ventilated patients.
ii) To evaluate the impact of LVAP on clinical outcomes, including mortality, duration of mechanical ventilation, and length of ICU stay.
iii) To determine the microbial profile and antimicrobial resistance patterns of pathogens causing LVAP.

MATERIAL AND METHODS

- **STUDY DESIGN:** A single centre, hospital-based, 1:1, matched case-control study.
- **SETTING:** Critical Care Unit, SukhSagar Medical College, Jabalpur, Madhya Pradesh.
- **ETHICAL CONSIDERATIONS:** Ethical approval was obtained from the Institutional Ethics Committee of SukhSagar Medical College, Jabalpur.Patient confidentiality was maintained in accordance with ethical guidelines and data protection regulations.Participation in the study was voluntary, with the option to withdraw at any time without affecting patient care.
- **DURATION OF STUDY:** 12 months.
- **DEFINITIONS:LATE-ONSET VENTILATOR-ASSOCIATED PNEUMONIA (LVAP):** Pneumonia developing ≥96 hours after endotracheal intubation and mechanical ventilation, diagnosed by new or progressive infiltrates on chest radiographs along with at least two of the following:
  - Fever >38.3°C.
  - Leukocytosis>10,000 cells/mm³.
  - Purulent tracheobronchial secretions.
- **SAMPLE SIZE:** A total of 280 patients, with 140 cases and 140 controls.
- **CASES:** Patients who develop pneumonia after 96 hours of mechanical ventilation (meeting the criteria for late-onset VAP).
- **CONTROLS:** Patients on mechanical ventilation for at least 96 hours who do not develop pneumonia during their ICU stay.
- **MATCHING CRITERIA:** Controls were matched to cases based on the following:

i) APACHE II score (±5 points) at the time of mechanical ventilation initiation.
ii) Duration of mechanical ventilation prior to LVAP onset (controls ventilated for at least the same duration as the onset of LVAP in the matched case).

- **INCLUSION CRITERIA:** Patients aged ≥18 years admitted to the ICU who are on mechanical ventilation for at least 96 hours.

EXCLUSION CRITERIA

i) Patients with pneumonia prior to or within 96 hours of mechanical ventilation.
ii) Patients with incomplete clinical or microbiological data.

- **MULTIDRUG-RESISTANT (MDR) ORGANISMS:** Organisms resistant to at least three classes of antibiotics[5].
- **SAMPLING METHODOLOGY: Amatched case-control sampling method** was employed to select participants for this study[6]. The sample size was **280 participants** in total, consisting of **140 cases** and **140 controls**[7]. The participants were drawn from patients admitted to the Intensive Care Unit at SukhSagar Medical College, Jabalpur, who were on mechanical ventilation for at least 96 hours.

PARTICIPANT RECRUITMENT PROCESS

1. **SCREENING PHASE:** All patients admitted to the ICU and receiving mechanical ventilation were screened daily. Patients who had been intubated for at least 96 hours were assessed for signs and symptoms of LVAP.
2. **IDENTIFICATION OF CASES:** Patients who developed clinical and radiological signs of LVAP (pneumonia after 96 hours of mechanical ventilation) were identified as potential cases.
3. **IDENTIFICATION OF CONTROLS:** For each confirmed case, a control patient was identified who:

- Had been on mechanical ventilation for at least the same duration as the matched case prior to LVAP onset.

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- Had a similar APACHE II score (±5 points) at the time of mechanical ventilation initiation.
- Had not developed pneumonia during their ICU stay.

PROCEDURE OF DATA COLLECTION

1. **PATIENT SCREENING AND ELIGIBILITY ASSESSMENT:** All patients admitted to the Department of Critical Care at SukhSagar Medical College, Jabalpur, who were on mechanical ventilation were screened daily. Patients who had been on mechanical ventilation for at least 96 hours were identified and assessed for potential inclusion in the study. Eligibility was determined based on the inclusion and exclusion criteria.
2. **INFORMED CONSENT PROCESS:** Informed consent was obtained from all eligible participants or their legal representatives. The purpose, procedures, potential risks, and confidentiality measures of the study were explained in detail. Patients or their representatives were given the opportunity to ask questions before signing the consent form.
3. **DATA COLLECTION TOOLS AND DOCUMENTATION:** A standardized data collection form was used to capture all relevant information. Data were collected from patient records, bedside monitoring, clinical examinations, and laboratory reports.
4. **COLLECTION OF DEMOGRAPHIC DATA:** Information such as age, sex, and primary diagnosis at the time of ICU admission was recorded. The following clinical details were collected and documented:

- **APACHE II SCORE:** Recorded at the time of mechanical ventilation initiation to assess illness severity.
- **DURATION OF MECHANICAL VENTILATION:** Number of days the patient remained on mechanical ventilation.
- **DURATION OF ICU STAY:** Total number of days the patient stayed in the ICU.
- **COMORBIDITIES:** Presence of conditions such as chronic obstructive pulmonary disease (COPD), diabetes, and immunosuppression.
- **MEDICATION HISTORY:** Prior use of steroids, immunosuppressants, or antibiotics.
- **PROCEDURES:** Instances of re-intubation and requirement for tracheostomy.
- **CLINICAL OUTCOMES:** Recovery status, mortality, and discharge against medical advice (DAMA).

5. **MICROBIOLOGICAL DATA COLLECTION:** Tracheobronchial secretions were collected from patients with suspected LVAP and sent to the microbiology laboratory for culture and sensitivity testing. Significant microbial growth ($>10^5$ CFU/ml) was documented. The types of pathogens isolated and their antimicrobial resistance patterns, particularly multidrug-resistant (MDR) organisms, were recorded.
6. **BLOOD CULTURES:** Blood samples were collected when bacteremia was suspected and sent for culture. Results indicating the presence of bacteremia and the corresponding organisms were documented.
7. **CHEST RADIOGRAPHS:** Chest X-rays were performed to identify new or progressive infiltrates indicative of LVAP. Radiographic findings were documented and correlated with clinical signs.
8. **DAILY MONITORING AND CLINICAL ASSESSMENT:**Patients were monitored daily for signs of infection, including fever, leukocytosis, and changes in respiratory secretions. Clinical assessments were recorded throughout the ICU stay.

- **STATISTICAL ANALYSIS:**Descriptive statistics were used to summarize the demographic and clinical characteristics of the cases and controls. Categorical variables, such as sex, presence of comorbidities, and antimicrobial resistance patterns, were expressed as frequencies and percentages. Continuous variables, such as age, duration of mechanical ventilation, and length of ICU stay, were summarized as means and standard deviations or medians and interquartile ranges, depending on data distribution. To compare categorical independent variables (e.g., use of steroids, presence of bacteremia, re-intubation) between cases and controls, **McNemar's test** was used to account for the matched study design. For continuous independent variables that were not normally distributed (e.g., duration of mechanical ventilation and length of ICU stay), **Wilcoxon signed-rank test** was applied to assess differences between cases and controls. For normally distributed continuous variables (e.g., age), **paired t-tests** were used to compare the means between the two groups. A **p-value <0.05** was considered statistically significant for all tests.

RESULTS

In this study, several significant findings were observed among patients with late-onset ventilator-associated pneumonia (LVAP) compared to controls.Patients with LVAP had a significantly higher prevalence of **prior use of steroids or immunosuppressants** (18.6% in cases vs. 2.1% in controls; $p = 0.003$). Additionally, **re-intubation** was more common in LVAP cases (16.4%) compared to controls (3.6%; $p = 0.018$). **Bacteremia** was also significantly associated with LVAP, occurring in 27.1% of cases versus 5.0% of controls ($p = 0.001$).

In terms of clinical outcomes, patients with LVAP required a significantly **longer duration of**

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mechanical ventilation (median 16.5 days) compared to controls (median 11.0 days; $p < 0.001$). The **length of ICU stay** was also significantly extended in LVAP cases (median 21.0 days) compared to controls (median 16.0 days; $p = 0.046$). Furthermore, the **requirement for tracheostomy** was higher in LVAP cases (52.1%) compared to controls (28.6%; $p = 0.037$). Lastly, **mortality** was significantly higher in patients with LVAP (27.1%) compared to controls (14.3%; $p = 0.022$).These findings highlight the impact of LVAP on patient outcomes, particularly with regard to the increased need for prolonged ventilation, extended ICU stays, higher rates of tracheostomy, and increased mortality.

Table 1: Characteristics of Participants

	Cases(n=140)	Controls(n=140)	P-value
Demographic Profile			
Mean Age (years)	47.5 ± 15.8	50.2 ± 16.4	
Male-to-Female Ratio	2.5:1	2.0:1	
Diagnosis			
Cerebrovascular Accident (CVA)	7.9%	22.1%	
Multi-Organ Dysfunction	10.0%	17.1%	
Trauma	12.1%	14.3%	
Postoperative Status	10.0%	15.0%	
Encephalitis	5.7%	4.3%	
Other Medical Conditions	7.9%	7.7%	
Risk Factor			
Prior Use of Steroids/Immunosuppressants	18.6%	2.1%	0.003
Re-Intubation	16.4%	3.6%	0.018
Bacteremia	27.1%	5.0%	0.001
Diabetes Mellitus	**23.1%**	**25.0%**	**0.990**
Coma (GCS <6)	**48.1%**	**57.7%**	**0.424**
Smoking	**34.6%**	**28.8%**	**0.664**
Alcohol Consumption	**44.2%**	**25.0%**	**0.064**
Recent Hospital Admission	**29.3%**	**18.6%**	**0.091**
Outcome			
Duration of Mechanical Ventilation (days)	16.5 (11-22)	11.0 (7-15)	<0.001
Length of ICU Stay (days)	21.0 (14-29)	16.0 (10-21)	0.046
Requirement for Tracheostomy	52.1%	28.6%	0.037
Mortality Rate	27.1%	14.3%	0.022

The analysis of endotracheal aspirate cultures in patients with late-onset ventilator-associated pneumonia (LVAP) revealed that ***Acinetobacter* spp.** was the most frequently isolated pathogen, identified in **49.3%** of cases. This was followed by ***Pseudomonas* spp.**, which was found in **41.4%** of cases, and **Klebsiella pneumoniae**, present in **38.6%** of cases. Additionally, **Staphylococcus aureus** was isolated in **12.9%** of cases. These findings highlight that Gram-negative bacteria, particularly *Acinetobacter* and *Pseudomonas*, were the predominant pathogens associated with LVAP, indicating the need for targeted antibiotic therapy to address these resistant organisms.

Table 2: Microbiological Profile

Pathogen	Cases (%)
Acinetobacter spp.	49.3%
Pseudomonas spp.	41.4%
Klebsiella pneumoniae	38.6%
Staphylococcus aureus	12.9%

The study found a high prevalence of **multidrug-resistant (MDR) organisms** among the patients with late-onset ventilator-associated pneumonia (LVAP). **Overall Prevalence of MDR Organisms was 59.3%** of LVAP cases were caused by MDR pathogens. MDR *Acinetobacter* was identified in **75.0%** of LVAP cases where *Acinetobacter* was isolated. MDR *Pseudomonas* was found in **67.2%** of LVAP cases where *Pseudomonas* was identified. MDR *Klebsiella pneumoniae* and MDR *Staphylococcus aureus* were identified in a smaller proportion of cases.

DISCUSSION

This study explored the determinants, microbial profile, and clinical outcomes associated with late-onset ventilator-associated pneumonia (LVAP) among mechanically ventilated patients in a tertiary care ICU. The findings demonstrated that LVAP is

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significantly associated with prolonged mechanical ventilation, extended ICU stays, higher tracheostomy rates, and increased mortality, with ***Acinetobacter* spp.** and ***Pseudomonas* spp.** being the predominant multidrug-resistant (MDR) pathogens. These findings align closely with those reported in other studies conducted in similar settings.

RISK FACTORS

Several risk factors identified in the present study are consistent with those reported in other studies. In the present study, the prior use of steroids or immunosuppressants was significantly higher in LVAP cases (18.6% vs. 2.1%; $p = 0.003$). This finding aligns with the study by **Saravu*et al.* (2013)**, which also reported a significant association between steroid use and the development of VAP ($p = 0.004$)(8). The immunosuppressive effects of steroids increase susceptibility to infections by impairing host defense mechanisms. Re-intubation was identified as a significant risk factor in both the current study (16.4% in cases vs. 3.6% in controls; $p = 0.018$) and the study by **Saravu*et al.* (2013)** (17.3% vs. 1.9%; $p = 0.021$)[8]. Re-intubation increases the risk of introducing pathogens into the lower respiratory tract, which may lead to LVAP[9].

The current study found bacteremia to be significantly associated with LVAP (27.1% in cases vs. 5.0% in controls; $p = 0.001$). This result is supported by **Saravu*et al.* (2013)**, who reported bacteremia in 28.8% of VAP cases compared to 3.8% in controls ($p = 0.002$)(8). The presence of bacteremia may indicate systemic infection and complicate the course of LVAP.

The microbial profile in the present study, which identified ***Acinetobacter* spp.** (49.3%) and **Pseudomionas spp.** (41.4%) as the most common pathogens, mirrors findings from other research. In the study by **Saravu*et al.* (2013)**, ***Acinetobacter* spp.** (50%) and ***Pseudomonas* spp.** (40.4%) were the predominant pathogens causing LVAP. Similarly, the study by **Joseph *et al.* (2010)** reported a high prevalence of **Acinetobacter** (47%) and **Pseudomonas** (34%) in LVAP cases[10]. These findings underscore the persistence of Gram-negative bacteria as the leading cause of LVAP, particularly in ICUs where MDR pathogens are prevalent[11,12].

The current study reported that **59.3%** of LVAP cases involved MDR pathogens, with **MDR Acinetobacter** identified in **75%** and **MDR Pseudomonas** in **67.2%** of cases. This is consistent with **Saravu*et al.* (2013)**, who found **76.9%** of VAP cases caused by MDR organisms, with **MDR Acinetobacter** significantly associated with LVAP (76.2%; $p = 0.034$)[8]. The high prevalence of MDR pathogens complicates treatment and highlights the urgent need for robust antibiotic stewardship programs[9,13].

CLINICAL OUTCOMES

Patients with LVAP in the current study required significantly longer mechanical ventilation (median 16.5 days vs. 11.0 days; $p< 0.001$). **Saravu*et al.* (2013)** also reported prolonged mechanical ventilation in VAP cases (mean 16.08 days vs. 10.98 days; $p = 0.001$)[8]. **Rello*et al.* (2002)** similarly demonstrated increased ventilation duration in patients with VAP[14]. The median ICU stay was significantly longer in LVAP cases (21.0 days vs. 16.0 days; $p = 0.046$). This finding is consistent with **Saravu*et al.* (2013)**, where VAP cases had a mean ICU stay of 22.71 days compared to 17.04 days for controls ($p = 0.049$)[14]. Prolonged ICU stay increases healthcare costs and resource utilization, emphasizing the need for preventive measures[15]. Mortality in LVAP cases was **27.1%** in the current study, which is slightly lower than the **36.5%** mortality reported by **Saravu*et al.* (2013)**. **Chastre and Fagon (2002)** reported VAP-related mortality rates ranging from **24% to 50%**, with higher rates in cases caused by MDR organisms[16]. These findings highlight the significant impact of LVAP on patient survival[4,17].

CONCLUSION

The present study corroborates findings from other similar studies, emphasizing that LVAP is associated with identifiable risk factors, a predominance of MDR Gram-negative pathogens, and adverse clinical outcomes, including prolonged ventilation, extended ICU stays, and increased mortality. The consistent identification of ***Acinetobacter* spp.** and ***Pseudomonas* spp.** across studies reinforces the need for targeted antibiotic therapy, strict infection control practices, and robust antibiotic stewardship programs to mitigate the burden of LVAP in critical care settings. Future research should focus on novel preventive strategies and interventions to reduce the incidence and impact of LVAP.

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