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Original article

# Incidence, microbiology, and mortality of ventilation-associated pneumonia in a large Italian cohort of critically ill patients: results from the PROSAFE project

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ABSTRACT

*Objectives:* Despite preventive measures, ventilator-associated pneumonia (VAP) remains the most common healthcare-associated infection in the intensive care unit (ICU). VAP's striking incidence and impact are a leading cause of morbidity and prolonged ICU stay. This study focused on the characteristics and outcomes of patients diagnosed with ICU-acquired VAPs in Italian ICUs.
*Methods:* Data were drawn from the PROSAFE network, a prospective multicentric observational project conducted across 192 Italian ICUs (2014–2023). Clinical data were recorded following the European Centre for Disease Prevention and Control VAP definitions. The incidence rate was estimated, and multivariable logistic regression identified ICU mortality risk factors.
*Results:* The patients admitted to the included ICUs were 402 085. Among 122 430 classified at risk for VAP because of invasive mechanical ventilation (IMV) ≥48 hours, a total of 11 978 VAP cases were identified, corresponding to a prevalence of 9.8%. The incidence rate of VAP was 10.47 cases per 1 000 ventilator days (95% CI: 10.28–10.66).
Patients with VAP exhibited prolonged ICU stays (median: 23 days, Q1–Q3: 15–36) and high mortality (30.0%).
Microbiological profiling of VAP identified *Pseudomonas* spp. (21.0%), *Staphylococcus aureus* (20.2%), and *Klebsiella* spp. (20.1%) as the predominant pathogens. The logistic regression showed that older age, chronic liver and kidney diseases, multidrug-resistant organisms, and *Acinetobacter* spp. aetiology and duration of ICU stay before VAP were significantly associated with higher mortality.
*Discussion:* While confirming the overall high mortality of patients undergoing IMV, our findings highlight the significantly prolonged ICU stay in VAP patients, and the influence of multidrug-resistant organisms on VAP-related mortality. These insights emphasize the necessity for effective and timely preventive strategies, as well as the early identification of VAP aetiology. **Marta Colaneri, Clin Microbiol Infect 2025;31:1491**


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## Introduction

Ventilator-associated pneumonia (VAP) is a prevalent healthcare-associated infection in intensive care units (ICUs) [1], affecting up to 40% of patients on invasive mechanical ventilation (IMV) [2]. VAP incidence varies by region, ICU type, and diagnostic criteria [3], with rates of 1–2.5 cases per 1 000 ventilator days in North America [4] and 18.3 in Europe [5]. Patients with cancer and chronic obstructive pulmonary disease show elevated rates (24.5 and 19.9 per 1 000 IMV days) [6,7], and rates further increase in acute respiratory distress syndrome, or when receiving extracorporeal membrane oxygenation [8]. Hospital-acquired bacterial pathogens, particularly multidrug-resistant organisms (MDROs) like carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and Enterobacterales, and methicillin-resistant *Staphylococcus aureus*, dominate VAP aetiology [9,10], with resistance more common in late-onset cases and in regions with high MDRO burden [11]. The impact of MDROs on VAP outcomes is controversial [12], with mortality rates ranging from 1–1.5% [13] to 42% in acute respiratory distress syndrome [14]. VAP's independent contribution to mortality is unclear in patients with cancer [7] and traumatic brain injury [15]. However, VAP consistently prolongs IMV and ICU length of stay (LOS), increasing costs, and resource strain [1,16].

In this large multicentre study involving nearly 200 ICUs across Italy, we aimed to provide a comprehensive analysis of VAP in a setting with a high prevalence of MDROs. Specifically, the primary objective was to estimate VAP incidence across Italian ICUs. Secondary objectives included describing microbiological characteristics and their evolution in an MDRO-prevalent setting and identifying factors associated with intra-ICU mortality in patients with VAP.

## Methods

### Study design

This study is a multicentre, retrospective, observational analysis of the PROSAFE initiative (Promoting Patient Safety and Quality Improvement in Critical Care) [17].

### PROSAFE network

PROSAFE collects electronic data from over Italian ICUs participating to the Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GiViTI) network. Data entry is performed by ICU physicians using an electronic case report form synchronized with a central server for validation.

### Inclusion criteria

Data from January 1, 2013 to December 31, 2023 were analysed. All adult patients undergoing IMV for ≥48 hours in the ICU were eligible, including patients already receiving IMV at ICU admission. Specifically, patients with a confirmed VAP were selected to perform analyses on ventilator-free days (VFDs), microbiological characteristics, and risk factors for ICU mortality.

### Data collection

Variables included ICU- and patient-level characteristics. ICU data covered admission numbers and location, whereas patient data included demographics, admission indication, obesity, underweight status, and comorbidities. Microbiological data detailed ICU-acquired infections, pathogens, and resistance profiles. ICU outcomes included IMV duration, ICU stay, and mortality.

### Definitions

ICU-acquired VAP was defined as infection ≥48 hours post-IMV, per guidelines [18,19]. Early-onset VAP occurred within 96 hours; late-onset thereafter. The study included VAP and bloodstream infections. CRPA was resistant to meropenem or imipenem; carbapenem resistance in *Klebsiella* and *Acinetobacter* spp. was non-susceptibility to one carbapenem. MDROs included CRPA, carbapenem-resistant *Acinetobacter* spp. and Enterobacterales, methicillin-resistant *S. aureus*, and penicillin-resistant *Streptococcus pneumoniae*. Immunosuppression was defined by malignancies, transplantation, HIV, autoimmune diseases, or ICU clinician assessment via immunomodulatory therapy. Per Yehya et al. [20], VFDs were 0 if patients died within 28 days of IMV or remained ventilated >28 days. VFDs were 28 minus IMV duration post-VAP, with 0 if ≥ 28 days or deceased. Extubation was successful if IMV was not needed for ≥48 hours.

### Statistical analysis

To ensure data integrity, cross-variable checks were conducted, and inconsistent or missing data were reported in the electronic case report form. Data were valid if from ICUs with ≥90% complete admission records and ≥4 months of validated data yearly, per GiViTI metrics. Centres with <50% occupancy or heterogeneous monthly admissions were queried or visited by monitors. Valid ICU data were merged into an aggregated database. Categorical variables were reported as frequency and percentage, continuous variables as median, and Q1–Q3. Group differences were assessed using Kruskal–Wallis for continuous and Chi-square for categorical variables. VAP incidence was calculated via bootstrap sampling (4 000 iterations). Multivariable logistic regression identified ICU mortality risk factors, adjusting for expert-selected covariates. Model performance was evaluated using discrimination and GiViTI calibration tests. Details are provided in Supplementary Materials and Table S2.

Missing data were reported as observed without imputation. Percentages excluded missing values. For Simplified Acute Physiology Score II and Sequential Organ Failure Assessment scores, missing neurological component data were imputed separately for patients with and without neurological conditions to maximize discrimination of hospital and ICU mortality. Conditions distinguishing neurological from non-neurological patients are in the Supplementary Materials. Analyses used R version 4.0.3, with a 0.05 significance threshold.

### Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol of the PROSAFE project was approved by relevant local ethics committees at the participating centres. All patient data were pseudonymized before transmission to the GiViTI coordinating centre.

## Results

### Epidemiology of VAP

A total of 402 085 patients were admitted to the included 192 ICUs between 2014 and 2023. Among these, 122 430 were

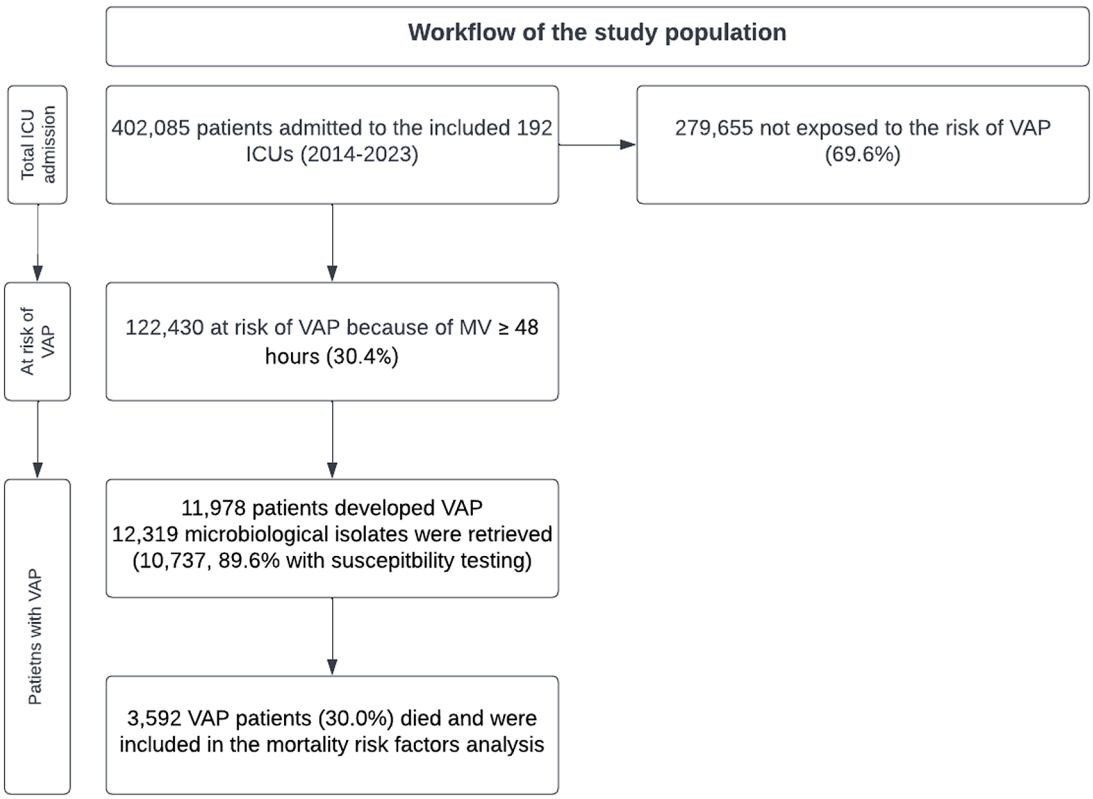


**Fig. 1.** Study flowchart. ICU, intensive care unit; MV, mechanical ventilation; VAP, ventilator-associated pneumonia.

classified at risk for VAP because of IMV ≥48 hours, and 11 978 patients developed VAP, with a prevalence of 9.8% (Fig. 1).

The VAP incidence rate was 10.5 (10.3–10.7) cases per 1 000 ventilator days.

The cumulative incidence of VAP as a function of exposure to IMV is reported in Fig. 2. Median exposure to IMV was 7 days (Q1–Q3: 4.0–12.0) before VAP, and more than two-thirds of episodes (8 149, 68.0%) were classified as late-onset VAP.

The sharpest increase in the number of VAP diagnoses was observed between days 3 and 4 of IMV, registering a 10-fold increase (from 1.9% to 20.0% of total VAP diagnosed). Moreover, the median ICU LOS before VAP diagnosis was 7.0 days (Q1–Q3: 4.0–12.0) among 11 978 patients. For patients who were hospitalized before ICU admission ($n$ = 5 184), the median combined hospital and ICU LOS before VAP onset was 13.0 days (Q1–Q3: 8.0–21.0).

### *Demographic, clinical, and microbiological characteristics of patients with VAP*

All patients included, with and without VAP, are described in Table 1.

Patients with VAP were more frequently males, and younger than 65 years old compared with patients without VAP ($p < 0.001$).

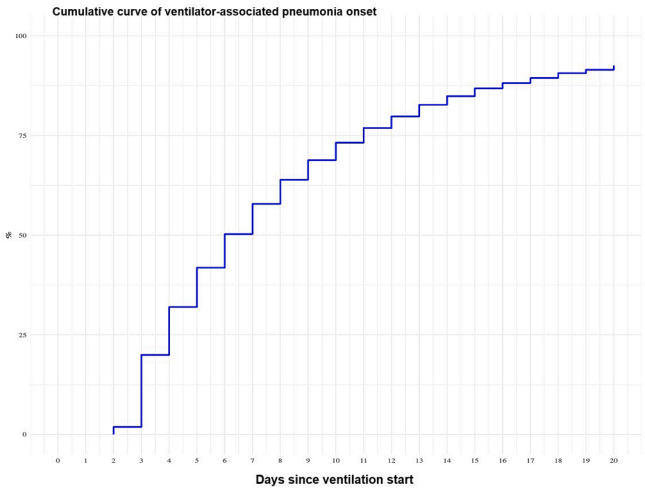


**Fig. 2.** Cumulative VAP incidence over time. VAP, ventilator-associated pneumonia.

**Table 1**
Demographic and clinic characteristic of patients admitted to ICU from 2014 to 2023

| Variable | Patients exposed to VAP onset ($N = 122\,430$) | Patients without VAP ($N = 110\,452$) | Patients with VAP ($N = 11\,978$) | p |
|---|---|---|---|---|
| Age >65 years, *n* (%) | 76 520 (62.5%) | 70 223 (63.6%) | 6 297 (52.6%) | *<0.001* |
| Sex male, *n* (%) | 77 242 (63.4%) | 68 657 (62.4%) | 8 585 (71.8%) | *<0.001* |
| *Missing* | *504* | *475* | *29* | |
| Ward of origin, *n* (%) | | | | *<0.001* |
| Medical | 24 231 (19.9%) | 21 918 (20.0%) | 2 313 (19.4%) | |
| Surgical | 26 270 (21.6%) | 24 337 (22.2%) | 1 933 (16.2%) | |
| Emergency room | 51 411 (42.3%) | 45 795 (41.7%) | 5 616 (47.1%) | |
| Other ICU | 14 089 (11.6%) | 12 689 (11.6%) | 1 400 (11.7%) | |
| High-intensity wards | 5 645 (4.6%) | 4 980 (4.5%) | 665 (5.6%) | |
| Missing | *784* | *733* | *51* | |
| Admission indication, *n* (%) | | | | *<0.001* |
| Medical intensive care | 71 272 (58.2%) | 65 083 (58.9%) | 6 189 (51.7%) | |
| Low-severity ICU admission[a] | 4 795 (3.9%) | 4 320 (3.9%) | 475 (4.0%) | |
| Surgical and postoperative care | 30 392 (24.8%) | 27 870 (25.2%) | 2 522 (21.1%) | |
| Trauma and emergency critical care | 15 971 (13.0%) | 13 179 (11.9%) | 2 792 (23.3%) | |
| BMI (median, IQR) | 25.9 (23.4, 29.4) | 25.9 (23.4, 29.4) | 26.1 (23.9, 29.4) | *<0.001* |
| Missing | *900* | *793* | *107* | |
| SOFA | 8.0 (5.0, 11.0) | 8.0 (5.0, 11.0) | 8.0 (6.0, 10.0) | *0.623* |
| Missing | *1* | *1* | *0* | |
| SAPSII | 46.0 (37.0, 58.0) | 47.0 (37.0, 59.0) | 43.0 (35.0, 54.0) | *<0.001* |
| *Missing* | *10 255* | *9335* | *920* | |
| Comorbidities, *n* (%) | | | | |
| Respiratory disease | 29 686 (24.2%) | 27 423 (24.8%) | 2 263 (18.9%) | *<0.001* |
| Neurologic disease | 23 550 (19.2%) | 21 844 (19.8%) | 1 706 (14.2%) | *<0.001* |
| Cardiovascular disease | 78 520 (64.1%) | 71 473 (64.7%) | 7 047 (58.8%) | *<0.001* |
| Hypertension | 64 571 (52.7%) | 58 631 (53.1%) | 5 940 (49.6%) | *<0.001* |
| Liver disease | 6 300 (5.1%) | 5 818 (5.3%) | 482 (4.0%) | *<0.001* |
| Renal disease | 13 207 (10.8%) | 12 323 (11.2%) | 884 (7.4%) | *<0.001* |
| Diabetes | 26 016 (21.2%) | 23 824 (21.6%) | 2 192 (18.3%) | *<0.001* |
| Autoimmune disease | 4 012 (3.3%) | 3 674 (3.3%) | 338 (2.8%) | *0.003* |
| Immunosuppression | 18 042 (14.7%) | 16 714 (15.1%) | 1 328 (11.1%) | *<0.001* |
| ICU-related procedures, *n* (%) | | | | |
| At least one surgical operation[b] | 47 347 (38.7%) | 42 058 (38.1%) | 5 289 (44.2%) | *<0.001* |
| Solid organ transplantation | 753 (0.6%) | 663 (0.6%) | 90 (0.8%) | *0.045* |
| Non-invasive ventilation | 9 195 (7.5%) | 8 110 (7.3%) | 1 085 (9.1%) | *<0.001* |
| Tracheostomy at admission | 6 248 (5.1%) | 5 755 (5.2%) | 493 (4.1%) | *<0.001* |
| Intra-ICU outcomes | | | | |
| Intra-ICU mortality, *n* (%) | 38 379 (31.3%) | 34 787 (31.5%) | 3 592 (30.0%) | *<0.001* |
| Missing | *1* | *1* | *0* | |
| Intra-ICU LOS (median, IQR) | 9.0 (5.0, 18.0) | 9.0 (5.0, 16.0) | 23.0 (15.0, 36.0) | *<0.001* |
| Missing | *4* | *4* | *0* | |
| Hospitalization outcomes, *n* (%) | | | | *<0.001* |
| Intra-hospital mortality | 45 395 (37.4%) | 41 304 (37.7%) | 4 091 (34.6%) | |
| Transferred to another hospital | 17 210 (14.2%) | 15 104 (13.8%) | 2 106 (17.8%) | |
| Transferred to another hospital regimen | 27 868 (23.0%) | 23 794 (21.7%) | 4 074 (34.4%) | |
| Nursing home | 1 982 (1.6%) | 1 864 (1.7%) | 118 (1.0%) | |
| Voluntary discharge | 544 (0.4%) | 518 (0.5%) | 26 (0.2%) | |
| Discharged at home | 28 260 (23.3%) | 26 846 (24.5%) | 1 414 (12.0%) | |
| Missing | *1171* | *1022* | *149* | |
| Intra-hospital LOS (median, IQR) | 21.0 (11.0, 36.0) | 20.0 (10.0, 34.0) | 33.0 (20.0, 52.0) | *<0.001* |
| Missing | *1165* | *1015* | *150* | |

BMI, body mass index; ICU, intensive care Unit; IQR, interquartile range; LOS, length of stay; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment Score; VAP, ventilator-associated pneumonia.

[a] Low-severity ICU admission: postoperative and/or ventilated patients who are supposed to be weaned in the next 24 hours.

[b] Thoracic surgery, cardiac surgery for bypass procedures, cardiac surgery for congenital conditions, cardiac surgery for acquired valvular disease, other cardiac surgery, surgery of the thoracic aorta, thoracic vascular surgery, abdominal vascular surgery, peripheral vascular surgery, neurosurgery, gastrointestinal surgery, oesophageal surgery, liver surgery, biliary tract surgery, pancreatic surgery, nephro/urological surgery, splenectomy, orthopaedic surgery, maxillofacial surgery, ear, nose, and throat surgery, ophthalmic surgery, plastic surgery, organ transplantation, organ donation, and other types of surgery.

In the VAP group, around half of the patients were admitted to the ICU from the emergency room department (5 616, 47.1%), with an indication of intensive medical care (6 189, 51.7%). Cardiovascular diseases (7 047, 58.8%) and hypertension (5 940, 49.6%) were the most frequently encountered comorbidities.

Four per cent (493, 4.1%) of patients with VAP already had tracheostomy at ICU admission, whereas 3643 (30.4%) patients with VAP underwent tracheostomization before VAP onset during their ICU stay.

Almost half of the patients with VAP (5 289, 44.2%) underwent at least one surgical procedure during the same hospital stay.

The Sequential Organ Failure Assessment score at ICU admission was a median of 8.0 (Q1–Q3: 5.0–11.0), with no significant difference observed between patients with VAP and patients without VAP (p 0.623).

### *Microbiological characteristics of VAP*

SARS-CoV-2 and other respiratory infections together were the most frequent infections at admission in patients with VAP (1 848 and 2 456, 15.4% and 20.5%, respectively), the former being

significantly more prevalent in this population when compared with patients without VAP (6 582, 6.0%, p < 0.001) (Table 2).

Considering VAP diagnostics, microbiological samples were obtained and analysed in 10 737 cases (89.6%) identifying 12 319 isolates. The most frequently isolated pathogen was *Pseudomonas* spp. (2 258, 21.0%), followed by *S. aureus, Klebsiella spp.,* and *Acinetobacter* spp. in 2 168 (20.2%), 2 157 (20.1%), and 1 046 (9.7%) of cases, respectively (Figs. 3(a) and (c)). Differently, carbapenem resistance was most frequent in *Acinetobacter* spp. (898, 85.9%), followed by *Klebsiella* and *Pseudomonas* spp. isolates (554 and 513, 25.6% and 22.7%, respectively) as shown in Fig. 3(b), whereas more than one-in-four *S. aureus* strains were methicillin-resistant (563, 25.9%, Fig. 3(d)). Although *Acinetobacter* spp. peaked during the COVID-19 pandemic, and it is currently declining, *Pseudomonas* spp. and *Klebsiella* spp. are steadily growing over time.

Twenty per cent (2 469, 20.7%) of patients with VAP had a concomitant bloodstream infections sustained by the same pathogen causing the VAP episode.

Complete data on pathogens prevalence and resistance patterns in VAP episodes are presented in Supplementary Materials, Table S2.

### *ICU and hospitalization outcomes of patients with VAP*

Median ICU LOS was 23 days (Q1–Q3: 15–36) for patients with VAP, compared with 9 days (Q1–Q3: 5–16) for patients without VAP (p < 0.001). Patients with VAP also had a longer intra-hospital LOS (median: 33 days, Q1–Q3: 20–52) compared with patients without VAP (20 days, Q1–Q3:10–34, p < 0.001).

Thirty per cent (3592, 30.0%) of patients died during ICU stay in the VAP group, less than in the group of patients without VAP (34 787, 31.5%, p < 0.001). Similarly, 34.6% (4 091) of patients with VAP died during hospitalization, compared with 37.7% (41 304) of those without VAP (p < 0.001). At 28 days from the diagnosis of VAP, 1 610 (13.6%) patients did not achieve spontaneous breathing; in the VAP population, mean VFDs were 8 (±10).

A shorter mean VFDs (7 ± 10 days vs. 9 ± 10 days, p < 0.01) was observed in the subgroup of patients with VAP caused by MDRO, compared with non-drug-resistant pathogens.

### *Risk factors for ICU mortality of patients with VAP*

Many factors significantly increased the intra-ICU mortality risk in patients with VAP, as shown in Fig. 4. Regarding demographic and clinical characteristics, the mortality risk increased by 39% for every 10 years of age (OR 1.4, CI: 1.3–1.5); underweight patients also had a significantly higher mortality risk (OR 1.7, CI: 1.3–2.2), as well as those with pre-existing diabetes, lung, liver, and end-stage renal diseases (ORs 1.2, 1.2, 1.9, and 2.5, respectively).

Mortality in patients with VAP was higher in episodes caused by MDROs (OR 1.3, CI: 1.2–1.5), compared with non-drug-resistant pathogens, as well as when *Acinetobacter* spp. was isolated (OR 1.9, CI: 1.5–2.2), regardless of resistance profiles. On the other hand, VAP episodes sustained by Enterobacterales and *S. aureus* carried a lower mortality risk (ORs 0.8 and 0.7, respectively). SARS-CoV-2 infection was significantly associated with a higher risk of death in patients with VAP (OR 2.4, CI: 2.0–2.8). Lastly, mortality risk was higher the most in patients already receiving IMV or vasoactive drugs at the time of VAP diagnosis (ORs 3.5 and 2.3, respectively) and when VAP was diagnosed after more than 4 (OR 2.7) and 9 (OR 4.2) ICU days. On the other hand, ICU admission for all causes other than intensive medical care, particularly trauma (OR 0.3, CI: 0.3–0.4), resulted in a reduced risk of mortality in patients with VAP.

The model showed good discrimination (area under the curve = 0.763) with a calibration p value of 0.07.

## Discussion

In this large, multicentre retrospective study involving nearly 12 000 cases of VAP across 192 ICUs in Italy, we observed a high incidence of late-onset VAP and a predominance of MDROs and highlighted clinical and microbiological factors significantly affecting intra-ICU mortality. The overall VAP incidence was 10.5 cases per 1 000 ventilator days, lower than the 13.48 cases per 1 000 ventilator days reported by the European Centre for Disease Prevention and Control across 14 countries [5], but higher than North America, likely because of variations in infection control protocols. Late-onset VAP, accounting for 68% of cases, underscores the risk associated with prolonged IMV, including extended exposure to invasive devices and nosocomial pathogens [21].

We observed a sharp rise in VAP diagnoses between days 3 and 4 of IMV, underscoring early prevention needs, like extubation assessments within 72 hours [22]. Despite ICUs likely following VAP prevention bundles (not systematically recorded), we believe consistently applying these precocious measures may reduce early-onset VAP [4].

About half of patients with VAP had cardiovascular disease and hypertension, whereas one-fifth were obese and with prior respiratory conditions, and known VAP risk factors [5,6]. Moreover, patients with VAP were more frequently admitted from emergency departments, suggesting the potential for underlying instability predisposing to this infection.

Although microbiological confirmation is strongly encouraged in VAP, it is not always possible, frequently leading to promptly start of an empiric therapy, relying on local resistance. In this context, we found a high percentage of microbiological confirmation in VAP episodes (nearly 90%), with *Pseudomonas spp.*, *S. aureus,* and *Klebsiella spp.* being the most frequent pathogens, as previously reported in the literature, emphasizing the critical role of *S. aureus* and opportunistic Gram-negative bacteria in ventilator-associated infections [1,23]. Moreover, carbapenem-

**Table 2**
Infections at ICU admission

| Variable | Patients exposed to VAP onset (*N* = 122 430) | Patients without VAP (*N* = 110 452) | Patients with VAP (*N* = 11 978) | p |
|---|---|---|---|---|
| Infection type at ICU admission, *n* (%) | | | | |
| Central nervous system infection | 1 679 (1.4%) | 1 570 (1.4%) | 109 (0.9%) | *<0.001* |
| Respiratory infection (pneumonia, pleuritis, empyema) | 25 174 (20.6%) | 22 718 (20.6%) | 2 456 (20.5%) | *0.869* |
| Intra-abdominal infection | 10 564 (8.6%) | 10 084 (9.1%) | 480 (4.0%) | *<0.001* |
| Skin and soft tissue infection | 2 457 (2.0%) | 2 323 (2.1%) | 134 (1.1%) | *<0.001* |
| Bone and joint infection | 423 (0.3%) | 385 (0.3%) | 38 (0.3%) | *0.579* |
| SARS-CoV-2 infection | 8 430 (6.9%) | 6 582 (6.0%) | 1 848 (15.4%) | *<0.001* |

ICU, intensive care unit; VAP, ventilator-associated pneumonia.

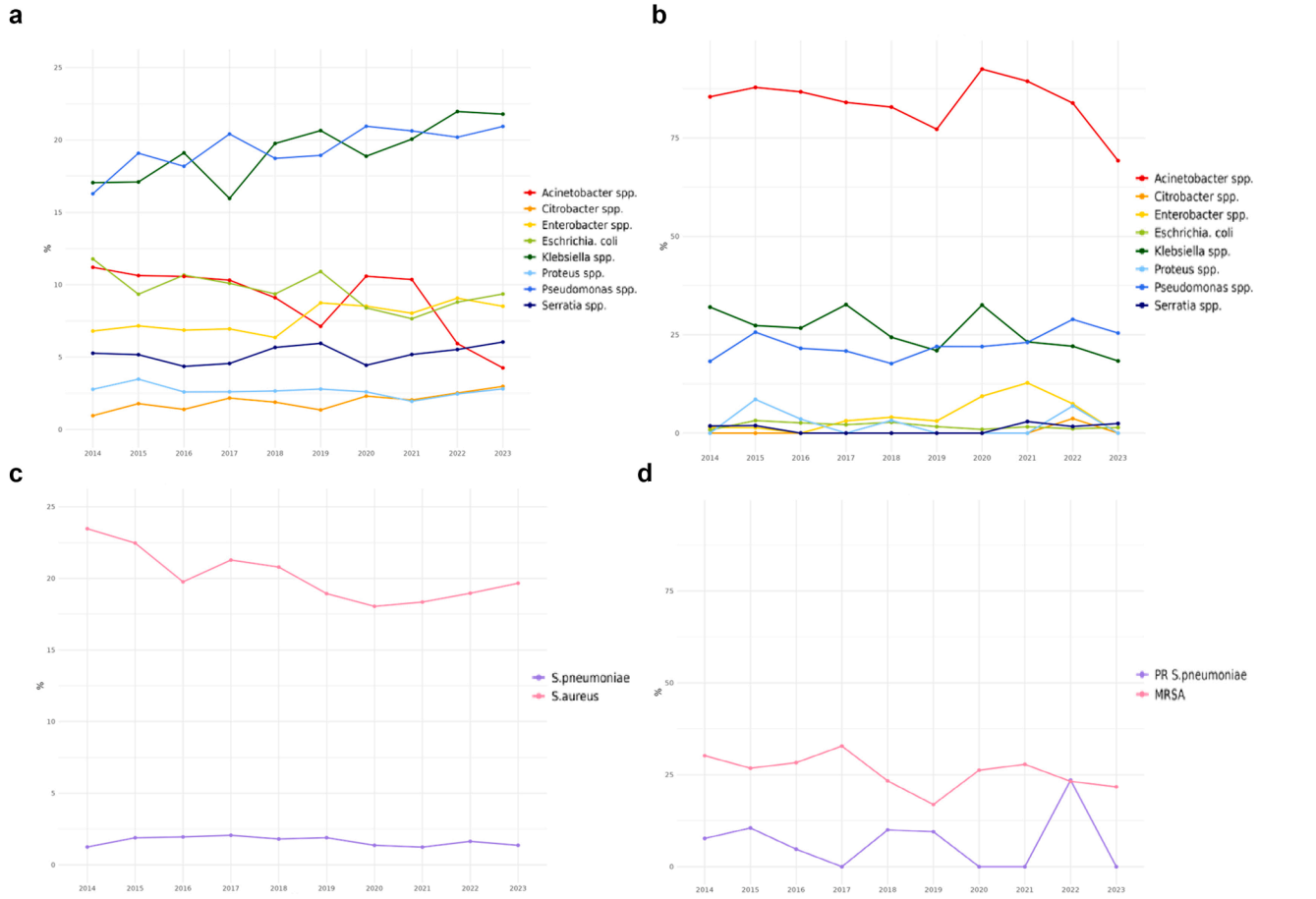


**Fig. 3.** Gram-negative (a) and gram-positive (c) bacteria isolated in VAP episodes, and relative antimicrobial resistance profiles (b and d, respectively) over time. MRSA, methicillin-resistant *Staphylococcus aureus*; PR, penicillin-resistant; *S. aureus, Staphylococcus aureus*; *S. pneumoniae, Streptococcus pneumoniae*; VAP, ventilator-associated pneumonia; VR, vancomycin resistant.

resistance was strikingly high in *Acinetobacter* spp., which has emerged as a major cause of outbreaks of healthcare-associated infections in Italy over the last decade [24].

Overall, the mortality rate was high, with about one-third (31.3%) of patients dying during their stay, confirming the current debate on VAP-associated mortality [25], while aligning with the rates of 20–50% described in the literature [11]. The better outcomes observed in patients with VAP compared with patients without VAP may be attributed to their younger age and lower burden of severe comorbidities. Additionally, they are more frequently admitted to the ICU for trauma or surgical complications, which generally have a more favourable prognosis than other severe medical conditions.

Patients with VAP had notably longer LOS, with median hospital and intra-ICU stays of 33 and 23 days, respectively, compared with 20 and 9 days for patients without VAP, consistent with previous results, which estimate that VAP episodes are associated with an additional 7–10 days of ICU stay [26].

Several factors independently increased mortality risk, including older age, underweight status, and chronic comorbidities such as diabetes, liver disease, pulmonary conditions, and end-stage renal disease. These comorbidities are known predictors of poor outcomes in critically ill patients and are unsurprisingly linked to higher mortality in VAP cases [27].

Moreover, SARS-CoV-2 infection was associated with a doubled risk of mortality in patients with VAP regardless of MDRO presence, as already described in both Italian and European studies [16,28].

The increased risk of mortality from infections caused by MDROs and *A. baumannii* emphasizes the role of antimicrobial resistance in poor clinical outcomes. CRAB is a significant Italian issue, with the highest European prevalence [18] and limited therapeutic options. CRAB rates increased during the COVID-19 pandemic [29], but Italy is not an isolated case, since the CDC reported this pathogen as the cause of approximately 7 000 infections and 500 deaths annually in the United States. Nonetheless, debate remains about whether all *A. baumannii* isolates in VAP cases represent true infections or merely airway colonization and a proxy of the patient's impaired immune system.

The observed increased mortality risk with the use of IMV and longer ICU stay before VAP diagnosis (beyond 4 and 9 days) highlights the role of patient haemodynamic status and ventilatory dependence in clinical outcomes. This is likely because of the cumulative effects of prolonged IMV on immune suppression [27], systemic inflammation, increased haemodynamic instability, and exposure to nosocomial MDROs. In our opinion, identifying the critical window of heightened risk enables more targeted interventions, such as early sedation breaks and mobility protocols, potentially improving outcomes for high-risk patients.

Finally, patients who experienced VAP episodes with MDRO pathogens had fewer VFDs, highlighting the unsurprisingly significant impact of antimicrobial resistance on weaning and recovery

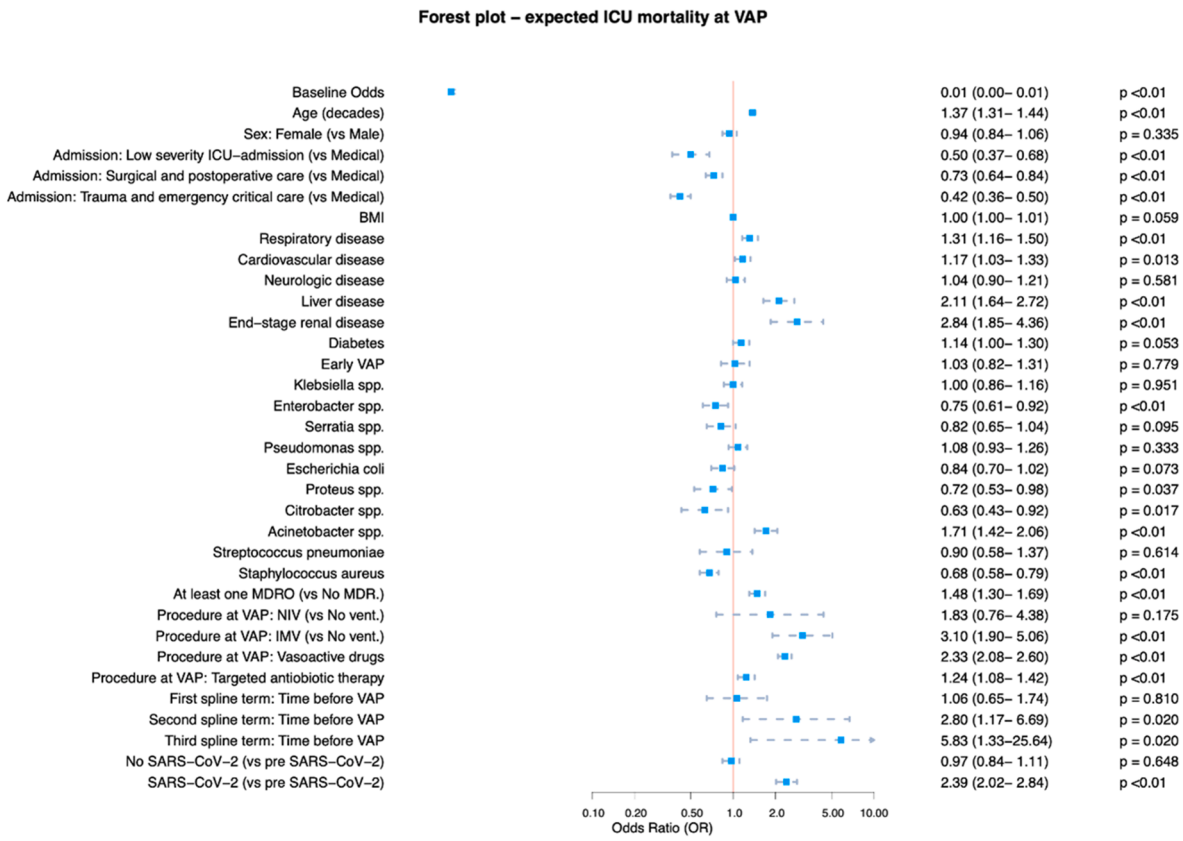


**Fig. 4.** Risk factors for mortality in patients with VAP. BMI, body mass index; early VAP, VAP episode diagnosed within the first 96 hours of MV; first spline term, ICU stay before VAP of 1–4 days; ICU, intensive care unit; IMV, invasive mechanical ventilation, MDR: multidrug-resistant; MDRO, multidrug-resistant organism; NIV, non-invasive ventilation; second spline term, ICU stay before VAP of 5–9 days; third spline term, ICU equal or more than 10 days; VAP, ventilator-associated pneumonia.

processes. This further underscores the importance of antibiotic stewardship and surveillance programmes, which may help limit the spread of MDROs, facilitating earlier ventilator liberation.

A major strength of this study is its large sample size, multicentre design, and extended timeframe, enhancing the generalizability of findings across Italian ICUs. The inclusion of nearly 12 000 cases provides robust epidemiological insights into VAP incidence, risk factors, and outcomes. Moreover, the study offers valuable data on MDRO infections, which is crucial for guiding infection control and antimicrobial stewardship practices.

However, some limitations must be acknowledged. As a retrospective study, selection and reporting biases are inherent. Additionally, data on the presence of sepsis and septic shock at the time of VAP diagnosis were not systematically collected in the PROSAFE database. Similarly, data on antibiotic appropriateness and timing, as well as data on available fast microbiology, were unavailable, limiting assessments of early diagnosis and targeted therapy's impact on survival and LOS. Furthermore, variability in ICU resources, infection prevention protocols, and clinical management practices across participating centres may have influenced results. Specifically, data on adherence to VAP prevention bundles were not collected systematically, precluding analysis of the relationship between bundle compliance and clinical outcomes. Another important limitation concerns the generalizability of our findings to settings outside of Southern Europe. Nevertheless, it should be noted that this study was conducted across a large number of ICUs and included a very high number of patients in a country with a particularly high burden of MDROs. Lastly, patients with VAP had a lower mortality rate than patients without VAP, likely because of survival bias, as they must first overcome the initial critical phase, whereas early deaths occur in more severe cases before VAP develops.

## Conclusions

Our study underlines the overall high mortality of patients undergoing IMV for more than 48 hours , the potentially significant impact of VAP on prolonged hospital and ICU stays, and the increased risk of poorer outcomes associated with VAP caused by MDROs. Early and aggressive preventive strategies, effective management of prolonged IMV, and prompt identification of MDRO infections are essential to improving clinical outcomes for patients with VAP.

## Author contributions

M.C., G.M., and S.F. were responsible for conceptualization. G.T., F.D., and S.F. were responsible for methodology. M.O. and G.M. were responsible for formal analysis and investigation. M.C., G.M., and G.S. were responsible for writing—original draft preparation. E.P., L.B., F.A., C.G., and V.S. were responsible for writing—review and editing. The Infection Surveillance Study Group of the Italian Group for Evaluation of Interventions in Intensive Care Medicine was responsible for resources. A.G., B.V., and S.F. were responsible for supervision. M.C., G.M., M.O., and S.F. contributed equally to this work.

## Transparency declaration

*Potential conflict of interest*

E.P., being the corresponding author, states that G.M. has received lecture or advisory board fees from Gilead, Thermofisher, 3M, Grifols; B.V. has received fees from Abbott, Accelerate Diagnostics, Ada, Advanz Pharma, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Diasorin, Emmegi Diagnostica, Gilead, InfectoPharm, Menarini, MSD Italia, Nordic Pharma, Pfizer, Shionogi, and Thermofischer Scientific.

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The complete list of Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (GiViTI, in English: Italian Group for Evaluation of Interventions in Intensive Care Medicine as defined above) referents who contributed to data collection and realization of the GiViTI project is available in the Supplementary Materials section of the paper.

The complete dataset is available via the corresponding author upon reasonable request.

Preliminary findings from this study will be presented at the ESCMID Global 2025 to be held in Vienna, Austria.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2025.05.026.

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