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Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models

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Abstract *Purpose:* Methods for estimating the excess mortality attributable to ventilator-associated pneumonia (VAP) should handle VAP as a time-dependent covariate, since the probability of experiencing VAP increases with the time on mechanical ventilation. VAP-attributable mortality (VAP-AM) varies with definitions, case-mix, causative microorganisms, and treatment adequacy. Our objectives here were to compare VAP-AM estimates obtained using a traditional cohort analysis, a multistate progressive disability model, and a matched-cohort analysis; and to compare VAP-AM estimates according to VAP characteristics. *Methods:* We used data from 2,873 mechanically ventilated patients in the Outcomerea® database. Among these patients from 12 intensive care units, 434 (15.1%) experienced VAP; of the remaining patients, 1,969 (68.5%) were discharged alive and 470 (16.4%) died. With the multistate model, VAP-AM was 8.1% (95% confidence interval [95%CI], 3.1–13.1%) for 120 days' complete observation, compared to 10.4% (5.6–24.5%) using a matched-cohort approach (2,769 patients) with matching on mechanical ventilation duration followed by conditional logistic regression. VAP-AM was higher in surgical patients and patients with intermediate (but not high) Simplified Acute Physiologic Score II values at ICU admission. VAP-AM was significantly influenced by time to VAP but not by resistance of causative microorganisms. Higher Logistic Organ Dysfunction score at VAP onset dramatically increased VAP-AM (to 31.9% in patients with scores above 7). *Conclusion:* A multistate model that appropriately handled VAP as a time-dependent event produced lower VAP-AM values than conditional logistic regression. VAP-AM varied widely with case-mix. Disease severity at VAP onset markedly influenced VAP-AM; this

may contribute to the variability of previous estimates.

Keywords Nosocomial pneumonia · Multistate models · Benchmarking · Logistic regression · Critically ill

Introduction

Nosocomial pneumonia is the most commonly reported infection in intensive care units (ICUs), with mechanically ventilated patients being at highest risk. The incidence of ventilator-associated pneumonia (VAP) has ranged from 8 to 28% [1]. VAP is associated with significant increases in hospital stay length, morbidity, and mortality [2]. In the United States, VAP was recently proposed as a quality-of-care indicator for ICUs.

The excess risk of death attributable to VAP varies considerably across studies, from 0 to 50% [3]. Four main factors contribute to this variability. First, the diagnosis of VAP is difficult to establish with complete certainty, as there is no pathognomonic finding or set of findings, and the surveillance definition developed by the Centers for Disease Control is both complex and subjective [4–6]. Second, antimicrobials are often started before samples are collected for microbiological tests [7]. Third, the patient populations vary across studies. Thus, studies have been done in trauma patients [8], patients with acute respiratory distress syndrome [9] or COPD [10], medical ICU patients [11], and general [2] ICU patients. Finally, adequacy of antimicrobial and timing of adequate antibiotic therapy may influence the estimates [3, 12, 13].

In addition to these factors, the statistical methods used may contribute to the variability in reported VAP-attributable mortality (VAP-AM) values. The risk of VAP increases with the duration of mechanical ventilation (MV). Therefore, MV duration is often used to match patients with and without VAP in matched-cohort studies [14]. However, with this method, the event of interest (e.g., VAP) is assumed to be present at study initiation, since each patient is classified either as a VAP patient or as a control, and conditional logistic regression is used to assess the risk of death associated with the event, which may bias the estimate of AM due to the matching [15]. Recently, a multistate model known as the progressive disability model was developed to take into account both the time-dependency of the risk factor (e.g., VAP) and the presence of competing risks (e.g., death and discharge) at each time point [16, 17].

Here, our purpose was to compare VAP-AM computed in the same population using either logistic regression or the progressive disability model on the overall cohort or using conditional logistic regression on a nested-matched cohort. The population was composed of patients entered into the Outcomerea® database. We also assessed the influence of VAP characteristics on VAP-AM.

Materials and methods

Data source

We conducted a prospective observational study using data entered into the multicenter Outcomerea® database from November 1996 to April 2007. The database was fed by 12 French ICUs, which entered data on admission features and diagnosis, daily disease severity, iatrogenic events, nosocomial infections, and vital status. Each year, these data were entered for a subsample of at least 50 patients who were older than 16 years and had ICU stays longer than 24 h. To obtain the random subsample, each participating ICU chose to take either consecutive admissions to selected ICU beds throughout the year or consecutive admissions to all ICU beds over a single month.

Data collection

Data were collected daily by senior physicians or trained clinical research assistants with the help of local investigators in the participating ICUs (see Electronic Supplement Material).

Quality of the database

All precautions were taken to assure a permanent quality of database, like formation of investigators in each ICU or data quality check. More details are available in the ESM (Electronic Supplementary Material).

In all the ICUs, as previously reported [12, 13, 18], VAP was suspected based on the development of persistent pulmonary infiltrates on chest radiographs combined with purulent tracheal secretions, and/or body temperature $\geq$38.5°C or $\leq$36.5°C, and/or peripheral blood leukocyte count $\geq 10 \times 10^9$/L or $\leq 4 \times 10^9$/L. The definite diagnosis of VAP required a positive culture result from a protected specimen brush ($\geq 10^3$ cfu/ml), plugged telescopic catheter specimen ($\geq 10^3$ cfu/ml), BAL fluid specimen ($\geq 10^4$ cfu/ml), or quantitative endotracheal aspirate ($\geq 10^5$ cfu/ml).

Study population

In this study, the data set consisted of longitudinal observations from the multicenter Outcomerea® database. Patients were included if they remained in the ICU for at least 48 h and received MV within 48 h after ICU

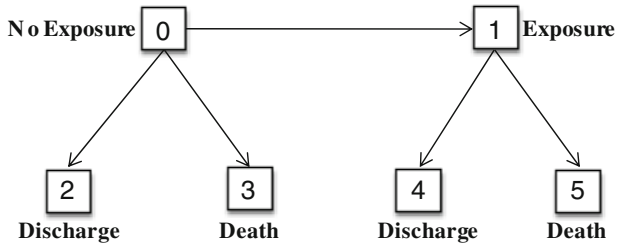


Fig. 1 Multistate progressive disability model. The *boxes* indicate the possible states and the *arrows* possible transitions in a given patient during the ICU stay. The full statistical model specifies the state structure and the form of the risk function for each possible transition. Of the six states, two (0 and 1) are transient states, i.e., states that are invariably followed by transition to another state. The other four states (2 through 5) are absorbing states, i.e., states from which further transitions cannot occur

admission. Patients were excluded if any of the following events did not occur: death in the ICU, discharge alive from the ICU, or the cessation of mechanical ventilation more than 48 h.

Data in the results section and Table 2 were obtained from 2,873 patients, corresponding to 40,524 ICU days. Median MV duration was 7 days (IQR, 4–14).

Statistical analysis

We compared three methods for estimating VAP-AM, namely, logistic regression (full cohort), multistate model [16, 17] (full cohort, Fig. 1), and conditional logistic regression (matched-cohort). The last two methods listed are described in the ESM.

We then performed a sensitivity analysis on the full cohort by using the multistate model to estimate VAP-AM according to case-mix and severity at ICU admission and according to VAP characteristics (methicillin-susceptible vs. methicillin-resistant *Staphylococcus aureus* VAP, ceftazidime-, ureidopenicillin-, and carbapenem-susceptible vs. -resistant *Pseudomonas aeruginosa* VAP, organ dysfunctions at VAP onset (LOD score divided in four groups according to quartiles), and MV duration at VAP onset (<8 days or ≥8 days).

All analyses were done using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). The multistate model used the package written by M. Wangler and J. Beyersman to assess changes in length of stay [19].

Results

Of the 2,873 patients, 434 (15.1%) experienced VAP. Table 1 shows the main patient characteristics in the full cohort. Patients with VAP were predominantly males in whom the main reason for ICU admission was more often acute respiratory failure and less often scheduled surgery, compared to patients without VAP. Crude ICU mortality was significantly higher in patients with VAP (119/434, 27.4%) than in patients without VAP (470/2,439, 19.2%). In the 470 patients who died without VAP, time from ICU admission to death was 3–73 days. In the 119 patients who died after acquiring VAP, median time from VAP onset to death was 16 days (IQR, 11–30). The main micro-organisms in the 434 episodes of VAP were *P. aeruginosa* ($n = 130$, 29%), *S. aureus* ($n = 89$, 20%), *Enterobacter* spp. ($n = 66$, 15%), and *Escherichia coli* ($n = 40$, 9%). Median MV duration at VAP onset was 7 days (IQR, 4–11). Of the 2,769 patients matched on duration of MV, 1,879 (67.9%) were discharged alive and 456 (16.4%) died (Fig. 2).

Crude estimates of attributable mortality

The unadjusted logistic regression model on the full cohort indicated that VAP was associated with an increased risk of death (OR, 1.58; 95%CI, 1.25–2.00; $P = 0.0001$). As all observations were complete, the logistic regression and PD models produced the same AM at the end of follow-up (8.1%; 95% CI [3.1%; 13.1%]) on the full cohort, but the PD model depicted variations in AM and the confidence band over time (Fig. 3). AM increased progressively to a plateau starting on day 78. We decided to set t at 120 days to derive summary measures and to maximize the number of transitions. Logistic regression analysis of the full cohort adjusted on SAPS II, male sex, admission category with three classes, and MV duration indicated a slightly higher estimate of the odds ratio of death (OR, 1.76; 95%CI, 1.33–2.32; $P < 0.0001$) compared to the unadjusted model.

Conditional logistic regression (matched population) versus progressive disability model (full cohort)

The conditional logistic regression model (on 2,769 patients) indicated that VAP was associated with an increased risk of death (OR, 1.54; 95%CI, 1.22–1.96; $P = 0.0004$). Adjusting on SAPS II, male sex, and admission category led to a small increase in the impact of VAP (adjusted OR, 1.71; 95%CI, 1.32–2.22; $P < 0.0001$).

Unadjusted VAP-AM estimated by conditional logistic regression was 10.4% [95%CI 5.6; 24.5], which was higher than the estimate provided by the progressive disability model (8.1% [95%CI 3.1%; 13.1%]).

Sensitivity analysis

The sensitivity analysis using the multistate model (Table 2) showed marked differences in VAP-AM across

Table 1 Patient characteristics

Variable	Patients with VAP: exposed ($n = 434$)	Patients without VAP: unexposed ($n = 2,439$)	P value[a]
Male gender, *n* (%)	315 (72.5)	1,518 (62.2)	0.005
Age, median	62.8	62.7	0.94
SAPS II, median	47.2	46.1	0.06
Admission category			
Medicine, *n* (%)	292 (67.3)	1,342 (55)	0.0001
Emergency surgery, *n* (%)	74 (17.1)	595 (24.4)	0.0004
Scheduled surgery, *n* (%)	68 (15.6)	337 (13.8)	0.36
History of immunosuppression			
Haematological malignancy, *n* (%)	20 (4.6)	81 (3.3)	0.22
Metastatic cancer, *n* (%)	20 (4.6)	153 (6.3)	0.21
AIDS, *n* (%)	11 (2.5)	39 (1.6)	0.26
Corticosteroid therapy, *n* (%)	82 (18.9)	454 (18.6)	0.94
Anticancer chemotherapy, *n* (%)	21 (4.8)	125 (5.1)	0.89
Main symptom at ICU admission			
Shock, *n* (%)	149 (34.3)	731 (29.9)	0.08
Coma, *n* (%)	100 (23.0)	533 (21.8)	0.62
Acute respiratory failure, *n* (%)	115 (26.5)	502 (20.5)	0.01
Other chronic illnesses			
Hepatic, *n* (%)	28 (6.4)	150 (6.2)	0.81
Cardiovascular, *n* (%)	73 (16.8)	344 (14.1)	0.21
Pulmonary, *n* (%)	70 (16.1)	330 (13.5)	0.23
Renal, *n* (%)	14 (3.2)	84 (3.4)	0.81
Diabetes, *n* (%)	49 (11.2)	202 (8.3)	0.04
ICU mortality, *n* (%)	119 (27.4)	470 (19.2)	0.0001

[a] Fisher test for qualitative variables and Kruskal–Wallis test for continuous variables

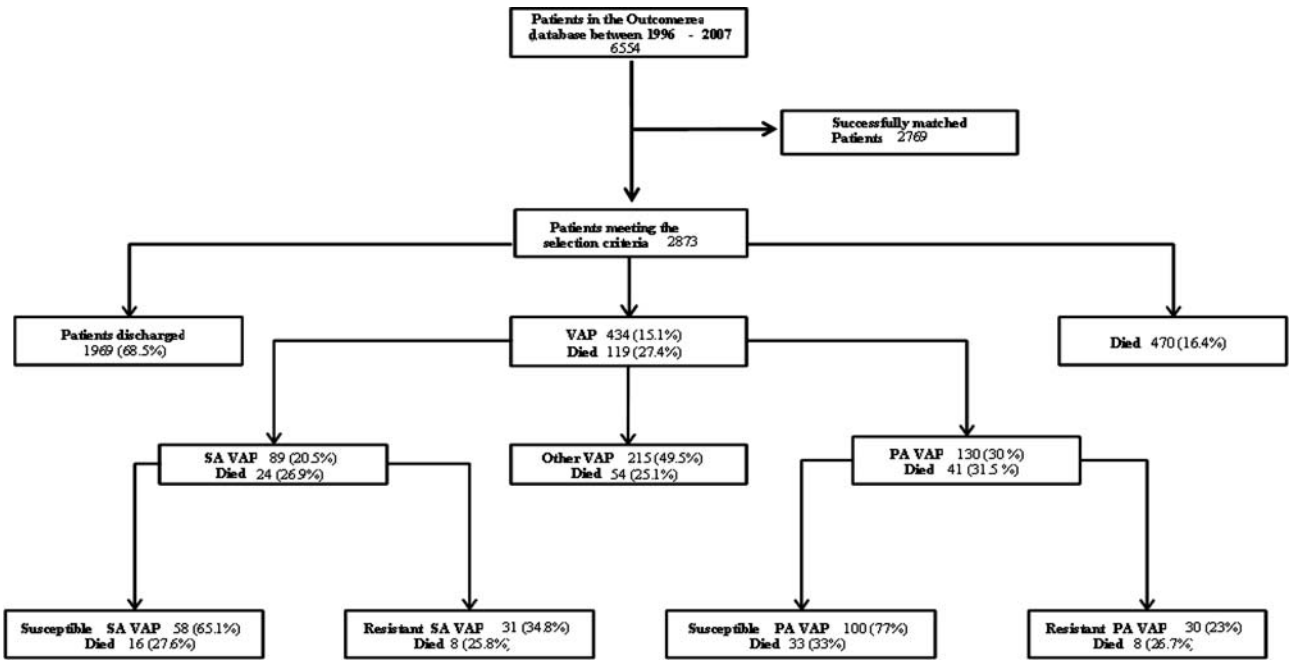


Fig. 2 Flow chart of the study patients. VAP, ventilator-associated pneumonia; SA VAP, VAP caused by *Staphylococcus aureus*; PA VAP, VAP caused by *Pseudomonas aeruginosa*

subgroups in the full cohort (2,873). Thus, VAP-AM was high and significantly different from zero in surgical patients and in patients with intermediate SAPS II values at ICU admission but was not different from zero in medical patients (Fig. 4, panel 2) or in patients with SAPS II values in the highest quartile (Fig. 4, panel 1).

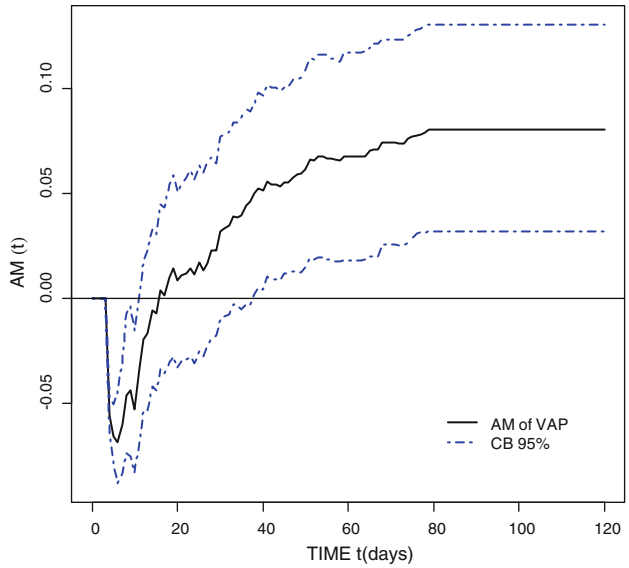


Fig. 3 Attributable mortality over time after mechanical ventilation onset. The *Y*-axis shows the attributable mortality of VAP on death and the *X*-axis the time since onset of mechanical ventilation. The continuous line represents VAP attributable mortality (AM) at time *t* after ICU admission. The dotted lines represent the 95% confidence band of the estimate. Of note, AM increased progressively to a plateau starting on day 78. The lower limit of the 95% confidence band became positive on day 35. The negative values at the beginning of the curve indicate a protective effect of VAP on mortality. This result is due to the underlying illnesses of some patients who did not have time to develop VAP before dying

VAP-AM was not significantly different from 0 in patients whose LOD score at VAP onset was lower than 5 but was 10.4% in patients whose LOD score was 6 or 7 and reached 31.9% in patients whose LOD score was greater than 7 (Fig. 4, panel 4). VAP-AM was higher in patients with late-onset VAP. High-level of resistance of *S. aureus* and *P. aeruginosa* did not affect VAP-AM.

Discussion

Using a large high-quality database and an appropriate statistical model, we found a significant VAP-AM of 8.1% (95%CI, 3.1–13.1). Although earlier studies found higher values of 15–50% [2, 3], our value is based on less biased assumptions and is consistent with the 10.6% value obtained in five German ICUs using a multistate model [17].

VAP-AM varied considerably with case-mix. Being a surgical patient or having an intermediate SAPS II score at ICU admission was associated with a higher VAP-AM value, whereas chronic co-morbidities had no effect. Greater disease severity as assessed by the LOD score at VAP onset was associated with a marked increase in VAP-AM. In the subgroup of patients with VAP due to *P. aeruginosa*, VAP-AM was higher when the organism was susceptible rather than resistant to ureidopenicillin. In contrast, no difference in VAP-AM was found between patients with methicillin-susceptible and methicillin-resistant *S. aureus* VAP. Finally, VAP-AM was higher in patients with late-onset VAP.

Occurrence of VAP is a time-dynamic process [17] and ICU discharge acts as a competing risk [20] when estimating the relationship between VAP and death. Both factors may bias the AM estimate.

Matching patients with and without VAP on MV duration and then performing conditional logistic regression is a widely used method to evaluate VAP-AM. This method is also used for other events that are dependent on the duration of exposure to a risk factor, such as bloodstream infections related to intravascular catheters. With this method, each patient is classified as being exposed (VAP) or unexposed (no VAP) and, in exposed patients, the data are handled as if the exposure were present at study initiation (although exposure status is determined at study completion). Thus, the excess risk of death associated with the exposure is assumed to be present throughout the ICU stay, that is, both before and after the occurrence of the exposure. In other words, the exposure is handled as a time-independent variable. If the exposure is in fact time-dependent (e.g., VAP or bloodstream infection, whose risk increases with MV and catheter duration, respectively), then a bias is introduced [21]. Thus, the impact of a time-dependent exposure on mortality is overestimated with this method (10.4% instead of 8.1% in our study). The progressive disability model, [16], in contrast, considers that the excess risk of death associated with the exposure exists only after the exposure occurs. In this multistate model, each patient goes through two or more states. Thus, at study initiation, all patients are classified as being in the unexposed state. Over time, some patients acquire the exposure of interest (here, VAP), thus switching to the exposed state, at different time points during the ICU stay (Fig. 1). Thus, the model fits reality far more closely than does the matched cohort design resulting in narrowest confidence intervals. The main advantage of using the multistate model for complete data is that mortality can be estimated over time. Thus, changes in the mortality rate over time can be detected. However, results from survival analysis and from simple logistic regression will coincide when the endpoints (discharge or death) are always observed (no excluded patients). In this situation, the multistate model and unadjusted logistic regression provide the same AM (because of the properties of the Aalen-Johansen multistate estimator used, see reference [22] for details). On the contrary, if no events of interest are observed (for example in the case of censoring after a fixed time-point), the progressive disability model will provide very different estimates of AM (on day 28, for example, the estimated VAP-AM in our study was 2.46%, 95%CI [−2.86–5.54%], Fig. 3) [23, 24].

Table 2 Attributable mortality estimated by the multistate model according to the characteristics of ventilator-associated pneumonia

	No VAP	VAP	Death without VAP *n* (%)	Death with VAP *n* (%)	Progressive disability model	
					AM	95%CI
VAP (overall estimate)	2,439	434	470 (19.3)	119 (27.4)	0.081	[0.031; 0.131]
Estimates according to characteristics at ICU admission						
SAPS II $\leq$ 33	759	86	112 (3.9)	11 (12.8)	0.089	[0.021; 0.167]
33 < SAPS II $\leq$ 45	750	125	196 (11.4)	31 (24.8)	0.134	[0.064; 0.207]]
46 < SAPS II $\leq$ 58	679	116	242 (22.4)	32 (27.6)	0.052	[−0.042; 0.146]
SAPS II > 58	685	107	354 (43.7)	45 (42.1)	−0.007	[−0.101; 0.095]
Medicine	1,342	292	1,006 (25)	86 (29.5)	0.044	[−0.018; 0.107]
Surgery (elective or emergent)	1,097	142	963 (12.2)	33 (23.3)	0.110	[0.046; 0.180]
At least one chronic illness	1,021	192	770 (24.6)	63 (32.8)	0.082	[0.009; 0.157]
No chronic illness	1,418	242	1,199 (15.4)	56 (23.1)	0.075	[0.020; 0.124]
Estimates according to characteristics at VAP onset						
VAP caused by methicillin-susceptible *Staphylococcus aureus*	2,439	58	470 (19.3)	16 (27.6)	0.083	[−0.016; 0.194]
VAP caused by methicillin-resistant *Staphylococcus aureus*	2,439	31	470 (19.3)	8 (25.8)	0.065	[−0.025; 0.226]
VAP caused by susceptible *Pseudomonas aeruginosa*	2,439	100	470 (19.3)	33 (33)	0.137	[0.042; 0.235]
VAP caused by resistant *Pseudomonas aeruginosa*	2,439	30	470 (19.3)	8 (26.7)	0.074	[−0.087; 0.252]
LOD <3 at VAP onset	2,439	109	470 (19.3)	14 (12.8)	−0.064	[−0.127; 0.003]
LOD 3–5 at VAP onset	2,439	152	470 (19.3)	36 (23.7)	0.044	[−0.014; 0.116]
LOD 6–7 at VAP onset	2,439	91	470 (19.3)	27 (29.7)	0.104	[0.017; 0.196]
LOD >7 at VAP onset	2,439	82	470 (19.3)	42 (51.2)	0.319	[0.216; 0.424]
EOP (early-onset pneumonia)	2,439	235	470 (19.3)	59 (25.1)	0.058	[−0.002; 0.109]
LOP (late-onset pneumonia)	2,439	199	470 (19.3)	60 (30.2)	0.106	[0.046; 0.186]

VAP ventilator-associated pneumonia, *AM* attributable mortality computed using the progressive disability model, *95%CI* 95% confidence interval, *SAPS II* Simplified Acute Physiology Score version II at admission (33, 45, and 58 separate the four quartiles), *LOD* Logistic Organ Dysfunction score at VAP onset (3, 5 and 7 separate the four quartiles)

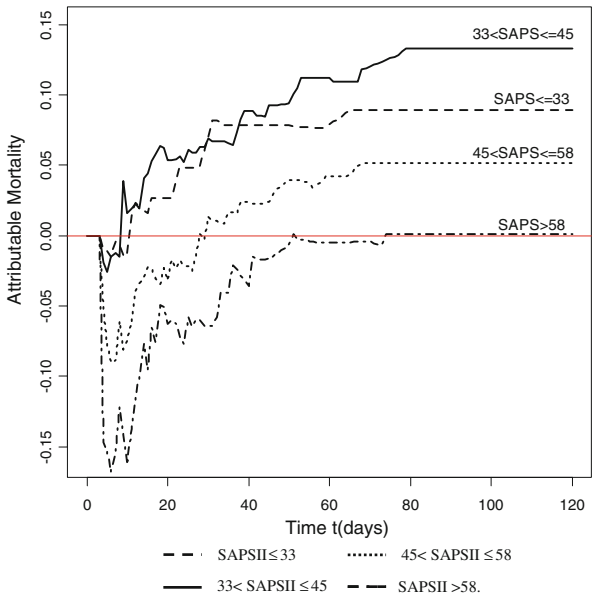
The negative AM values during the first few ICU days indicated a protective effect of VAP on mortality. This surprising result was due to underlying illnesses in some of the patients, in whom the time to death was too short to allow the development of VAP.

At present, the progressive disability model allows the evaluation of a single exposure and does not allow multiple adjustments. We therefore performed subgroup analyses to assess the impact of VAP characteristics on VAP-AM. In the numerous previous studies of VAP-AM, the estimates varied widely, as did the definition of VAP [2], case-mix, and distribution of causative micro-organisms. We found an interaction between the severity score (SAPS II) at ICU admission and VAP-AM. Thus, VAP-AM was greatest in the subgroup of patients with SAPS II scores in the 33–45 range at ICU admission and nonexistent in the subgroup with the highest SAPS II scores ($\geq$59). Similarly, in an earlier study, VAP was associated with an increase in the OR for death only in patients whose admission APACHE II score was between 11 and 29; however, MV duration was not taken into account in the analysis [25]. Another study showed that hospital-acquired bloodstream infections had no impact on mortality in patients with APACHE II scores greater than 20, whereas a highly significant impact was found in the less severely ill patients [26]. These data suggest that, in patients with a very high likelihood of death due to the severity of the acute illness, the added effect on mortality of experiencing VAP may be negligible. At the other end of the spectrum, patients with low disease severity may be able to mount an adequate immune response to the VAP-causing organism, so that VAP has little effect on mortality. Toward the centre of the spectrum, in contrast, patients with intermediate disease severity experience a marked increase in mortality in the event of VAP.

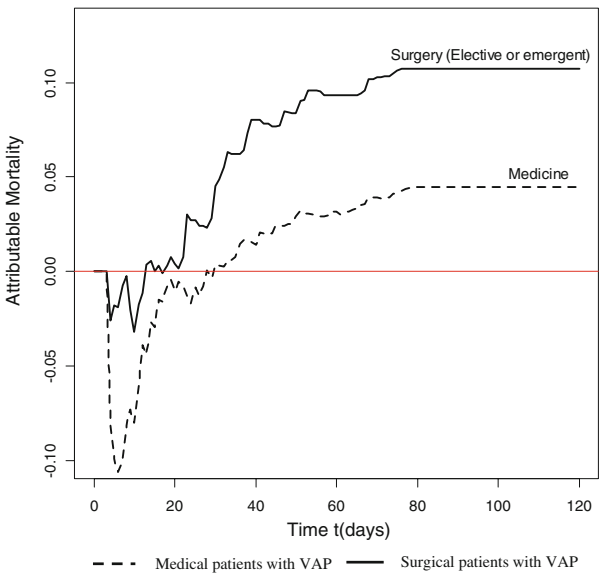
The VAP-AM was higher in surgical patients compared to medical patients. A difference in AM between medical and surgical patients has already been reported [27] with opposite conclusions. This difference may be due to difference in disease severity at admission or to other differences in case-mix and needs to be further explored.

Late-onset VAP is reported to be associated with higher mortality rates more often than early-onset VAP [13]. A likely explanation is the greater prominence of multidrug-resistant microorganisms among late-onset cases [6, 28, 29]. In one study, observed mortality in patients with late-onset VAP was twice that predicted based on the SAPS II (51.7 vs. 26.7%, yielding a 25% difference ascribable to VAP), whereas no difference was

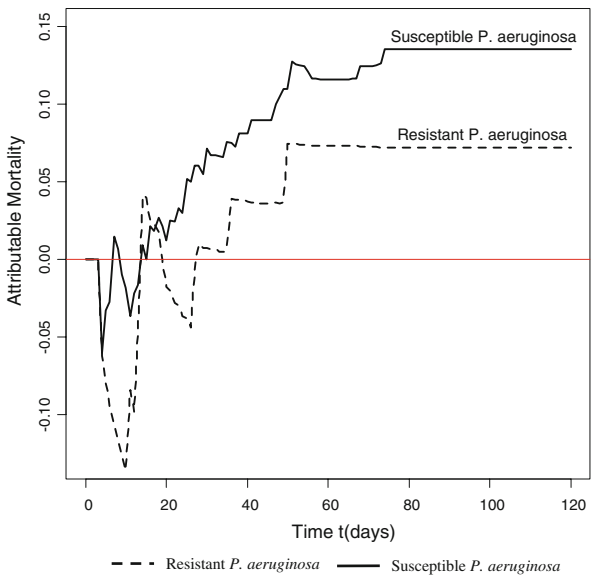
Panel 1. VAP-AM over time according to the patient severity at ICU admission.



Panel 2. VAP-AM over time in medical and surgical patients.



Panel 3. VAP-AM over time according to the susceptibility of *Pseudomonas aeruginosa* strains.



Panel 4. VAP-AM over time according to the severity of patient at VAP onset.

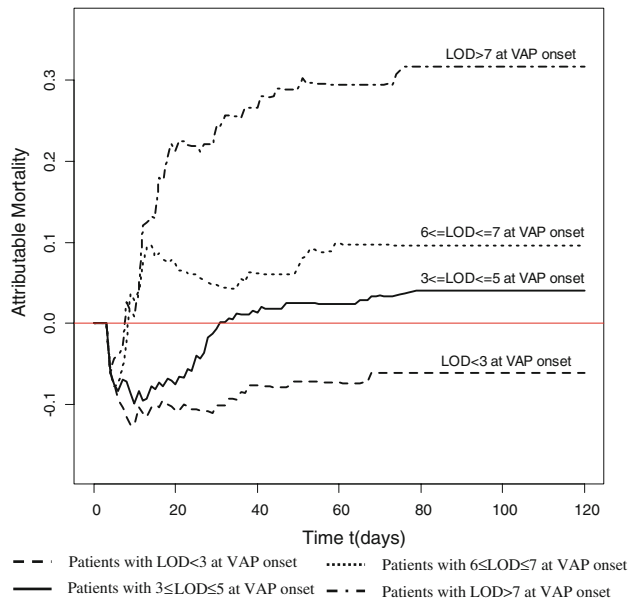


Fig. 4 Mortality attributable to ventilator-associated pneumonia (VAP-AM) over time after mechanical ventilation in several patient subgroups. At each time *t*, attributable mortality is defined as the probability of death if VAP occurs minus the probability of death if VAP does not occur

observed in patients with early-onset VAP [6]. However, this finding is probably ascribable to the lack of accuracy of mortality predictions in patients with ICU stays longer than 7 days (the population exposed to late-onset VAP) [30]. In our study, which took into account the time from ICU admission to VAP, VAP-AM was considerably lower for early-onset VAP (5.8%) than for late-onset VAP (10.6%).

We found that VAP due to methicillin-resistant *S. aureus* was not associated with excess mortality compared to VAP due to methicillin-susceptible *S. aureus*, in keeping with other studies that took into account the time

from ICU admission to VAP [31, 32]. Interestingly, VAP-AM was not higher when the causative organism was *P. aeruginosa* resistant to ureido/carboxypenicillin, ceftazidime, or imipenem than when the organism was susceptible to these antimicrobials. Many in vitro studies have established that the multidrug-resistance efflux pumps encoded by the *P. aeruginosa* genome are associated with decreased expression of the type III secretion system, which is involved in the pathogenic effect of the organism [33]. This mechanism might explain our finding that resistant *P. aeruginosa* was not associated with excess mortality compared to susceptible strains. However, we did not routinely seek to identify specific resistance mechanisms.

The factor that made the largest contribution to VAP-AM in our study was the LOD score at VAP onset. Similarly, earlier studies found that severity at VAP onset was the best predictor of mortality [4, 34, 35]. In our patients, an LOD score of 6 or 7 at VAP onset was associated with 10.4% VAP-AM and LOD scores higher than 7 with 31.9% VAP-AM, whereas no excess mortality from VAP was noted when the LOD score was less than 6 at VAP onset. If VAP is used for benchmarking, perhaps as a process indicator, [36] then VAP associated with LOD scores of 6 or more would deserve consideration, as this event is strongly associated with mortality. It would also be of interest to perform subgroup analyses in surgical patients and in patients with intermediate severity scores at ICU admission.

In conclusion, the progressive disability model provides a more accurate estimate of VAP-AM than do earlier methods, as it appropriately limits the impact of VAP to the portion of the ICU stay that follows VAP onset, describes variations in mortality over time, and involves informative censoring of ICU discharge. Our analysis of a high-quality database showed that VAP-AM was 8.1% overall. VAP-AM varied widely with case-mix, severity at admission, time to VAP onset, and severity of organ dysfunction at VAP onset. Bacterial resistance did not affect VAP-AM. The PD model unmasked potential sources of variation in AM. Other variables such as other case-mix issues, diagnostic techniques, and antibiotic timing need to be taken into account in future studies. New methods are under development to allow for further adjustment of AM estimates on multiple time-independent and time-dependent covariates.

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