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ORIGINAL

The association of cardiovascular failure with treatment for ventilator-associated lower respiratory tract infection

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Abstract

Purpose: Ventilator associated-lower respiratory tract infections (VA-LRTIs), either ventilator-associated pneumonia (VAP) or tracheobronchitis (VAT), accounts for most nosocomial infections in intensive care units (ICU) including. Our aim was to determine if appropriate antibiotic treatment in patients with VA-LRTI will effectively reduce mortality in patients who had cardiovascular failure.

Methods: This was a pre-planned subanalysis of a large prospective cohort of mechanically ventilated patients for at least 48 h in eight countries in two continents. Patients with a modified Sequential Organ Failure Assessment (mSOFA) cardiovascular score of 4 (at the time of VA-LRTI diagnosis and needed be present for at least 12 h) were defined as having cardiovascular failure.

Results: VA-LRTI occurred in 689 (23.2%) out of 2960 patients and 174 (25.3%) developed cardiovascular failure. Patients with cardiovascular failure had significantly higher ICU mortality than those without (58% vs. 26.8%; $p < 0.001$; OR 3.7; 95% CI 2.6–5.4). A propensity score analysis found that the presence of inappropriate antibiotic treatment was an independent risk factor for ICU mortality in patients without cardiovascular failure, but not in those with cardiovascular failure. When the propensity score analysis was conducted in patients with VA-LRTI, the use of appropriate antibiotic treatment conferred a survival benefit for patients without cardiovascular failure who had only VAP.

Conclusions: Patients with VA-LRTI and cardiovascular failure did not show an association to a higher ICU survival with appropriate antibiotic treatment. Additionally, we found that in patients without cardiovascular failure, appropriate antibiotic treatment conferred a survival benefit for patients only with VAP.

Trial registry: ClinicalTrials.gov, number NCT01791530.

Keywords: Pneumonia, VAP, SEPSIS, VAT, VA-LRTI, Antibiotic stewardship

Introduction

Lower respiratory tract infections (LRTIs) account for most nosocomial infections and patients admitted to intensive care units (ICUs) are at the highest risk, especially when invasive mechanical ventilation is provided [1, 2]. Ventilator-associated LTRI (VA-LRTI) comprises ventilator-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) [3–5]. VAP is

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universally accepted with defined guidelines for diagnosis and treatment, but it is thought that VAT represents an intermediate process from colonization to VAP, leaving its diagnosis and treatment under debate [6]. As an example, it remains controversial whether VAT should be treated with systemic antibiotics [7]. However, it is widely accepted that both VAP and VAT are associated with increased healthcare costs and are major drivers of antibiotic prescribing in the ICU [8, 9]. Notably, VAP is among the most common nosocomial infections in critically ill patients, with estimates of its incidence per 1000 ventilator days being higher among patients with more comorbidities, such as the elderly and immunocompromised [10], and varying considerably between countries.

The bacterial pathogens that cause VA-LRTI are frequently multi-drug resistant (MDR), which negatively impacts patient's outcome, because inappropriate antibiotic treatment is often prescribed [10, 11]. In an era of ever-increasing global antibiotic resistance and a dwindling development of new antibiotic drugs, a healthcare crisis may be imminent. Indeed, as Dame Sally Davies, England's Chief Medical Officer, said in a 2013 statement "…untreatable infection caused by antibiotic-resistant bacteria 'poses a catastrophic threat' to humans" and urged immediate global action [12]. However, the presence of resistant organisms and the use of inappropriate treatment are not the only independent risk factors for worse outcomes and mortality. The presence of cardiovascular failure has also repeatedly been shown to be an independent risk factor that may leave patients prone to worse clinical trajectories [13].

We hypothesized that appropriate antibiotic treatment in patients with VA-LRTI will reduce mortality in patients with cardiovascular failure. The aim of this study was to determine if appropriateness of antibiotic treatment was associated to a survival benefit in patients with cardiovascular failure and VA-LRTI.

Materials and methods

Study design and population

This was a pre-planned subanalysis of a large prospective cohort of 2960 critically ill patients who required mechanical ventilation for at least 48 h in eight countries in two continents. The base study was the Incidence and prognosis of VAT (TAVeM) study (ClinicalTrials.gov, number NCT01791530) [3]. Data related to diagnostic techniques, antibiotics, and general population characteristics have been published elsewhere [3, 14, 15]. Participating centers either received ethics approval from their institutions or ethics approval was waived (institutional review board number 2013515). Informed consent was waived, because of the observational nature of the study. Simplified Acute Physiology Score (SAPS) II scores were calculated on ICU admission (within the first 24 h), and Sequential Organ Failure Assessment (mSOFA) cardiovascular score was calculated at the time of VA-LRTI diagnosis (within the first 12 h). Patients with VA-LRTI diagnosis were analyzed based on the mSOFA cardiovascular score, to assess the presence of cardiovascular failure [16]. Cardiovascular failure was defined as follows: patients with a mSOFA score of 4 (dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norepinephrine > 0.1 μg/kg/min).

Take-Home Message

Appropriate antibiotic treatment is a major determinant of survival in patients with respiratory infections under mechanical ventilation. However, antibiotics appropriateness matters less in the most severe patients.

Definitions

A diagnosis of VA-LRTI was based on the presence of at least two of the following criteria: body temperature of more than 38.5 °C or less than 36.5 °C, leucocyte count greater than 12,000 cells per μL or less than 4000 cells per μL, and purulent endotracheal aspirate (ETA). Additionally, all episodes of VA-LRTI had to have a positive microbiological isolation in the ETA of at least 10^5 colony-forming units (CFU) per mL, or with bronchoalveolar lavage (BAL) of at least 10^4 CFU per mL, to be included in the final analysis. VAT was defined with the aforementioned criteria with no radiographical signs of new pneumonia; VAP was defined by the presence of new or progressive infiltrates on chest radiograph. Anterior–posterior portable radiographs were reviewed either by the attending physicians or radiologist. In case of disagreement, a third physician was asked to interpret the radiograph; however, the final diagnosis and antibiotic treatment were at the discretion of the attending physician. No CT scans or lateral radiographs were done for the diagnosis. We used serial chest radiographs to confirm new or persistent infiltrates as part of the diagnosis, but investigators were not masked to clinical characteristics, because of the observational nature of the study. In our study, we only included first episodes of microbiologically confirmed VA-LRTI occurring at more than 48 h after starting invasive mechanical ventilation. Resolution of either VAT or VAP was defined as the resolution of all diagnostic criteria. VAP was deemed as occurring subsequently to VAT, if it was diagnosed at the 96 h period

after diagnosis of tracheobronchitis and the same microorganism caused both the infections [17].

Microbiological identification and susceptibility tests were performed using standard methods. MDR pathogens were defined as those with acquired non-susceptibility to at least one agent in three or more antimicrobial categories [18]. Antibiotics were considered appropriate if the isolated pathogen was sensitive to at least one empirically prescribed antibiotic [13]. Immunocompromised patients were those with ongoing neoplasia, hematological malignancy, acquired immune deficiency syndrome (AIDS), allogeneic stem cell transplant, immunosuppressive drugs, or organ transplant [15].

Endpoints

The main endpoint was ICU mortality according to the presence or absence of cardiovascular failure and with the appropriateness of antibiotic treatment.

Other additional objectives were to determine the association of ICU mortality in VAP and VAT based on the presence or absence of cardiovascular failure and the appropriateness of antibiotic treatment.

Statistical analysis

Data are expressed as medians with interquartile ranges (IQRs), unless specified otherwise. Comparisons between groups were performed with unpaired Student's *t* test, one-way analysis of variance, Mann–Whitney *U*, or Kruskal–Wallis *H* tests for continuous variables depending on the data distribution. Chi-squared tests were used to compare categorical variables. Odds ratios (ORs) and confidence intervals (CIs) are reported where appropriate. In the present study, 2% (63/2960) of the eligible participants had at least one missing value for the set of variables considered relevant for the multivariate analyses. The fractions of missing values in individual variables were low (0.0–3.7%). We used multiple imputation by chained equations (MICE) to replace missing values and generate multiple completed datasets [19].

For attributing to mortality analysis, we included all patients in the TAVeM database. We incorporated all variables from univariate analysis with *p* values that were less than 0.1 or were clinically relevant into the regression analyses as potential predictor variables [age, mSOFA and SAPS II score, appropriate antibiotics, MDR isolates, presence of either infection (VAT or VAP), and type of patient (i.e., medical, surgical, trauma)]. We included all these variables, plus chronic kidney disease, diabetes and immunosuppression, in the model used to calculate ICU mortality as the dependent variable. Linearity assumption was tested for continuous covariates. To avoid overlap in the same regression model which could result in collinearity between the variables, logistic regression models, including each variable and baseline variables, were established and variables were selected using the backward stepwise regression method. We also calculated the Hosmer–Lemeshow goodness-of-fit ($p=0.25$). Collinearity between variables was checked by inspecting the correlation between them and by looking at the correlation matrix of the estimated parameters. The multicollinearity effect between risk factors in the model was detected using the variance inflation factor (VIF) and if VIF ≥ 5, excluded from the model. mSOFA was included in the model, but excluded from the final model due to collinearity. To account for center effects in this multicenter study with a binary outcome, we fitted a generalized estimating equation model with a logit effect of the presence or absence of cardiovascular failure [20].

After this first approach, we generate a propensity score optimal matching analysis to determine the effect of appropriate antibiotic treatment and to control the potential confounding factors in the entire population with VA-LRTI ($n=689$). Matching was done considering the following variables: Age, SAPS II, chronic kidney disease, diabetes, hematological malignancy, and admission type, because these variables did not have missing values and were considered clinically relevant to pair patients for the probability of receiving appropriate antibiotics [21, 22]. This approach allows us to study two comparable (close to identical) cohorts: (1) Appropriate antibiotic treatment group and (2) control group, which comprise those patients who did not receive appropriate antibiotic treatment. We first use optimal matching with replacement to compare outcomes between patients who have a similar distribution of all measured covariates. This method optimizes post-weighting balance of covariates between groups and, in this way, approximates the conditions of random site-of-treatment assignment [23]. To assess our propensity score adjustment, we checked for adequate overlap in propensity scores for both groups with cross-validation model. After optimal matching, a regression model for ICU mortality was built to determine the effect of appropriate antibiotic treatment in LRTI. This model was adjusted for appropriateness of antibiotic treatment, presence of cardiovascular failure and their interaction. Finally, for simplicity, we performed a simple logistic regression model in 689 patients with LRTI and assessed whether increasing mSOFA cardiovascular scores, from 0 to 4, would modulate the association between antibiotic appropriateness and predicted mortality.

All analyses were performed using R project version 3.4.0 with the tidyverse, randomForest, ggplot2, and

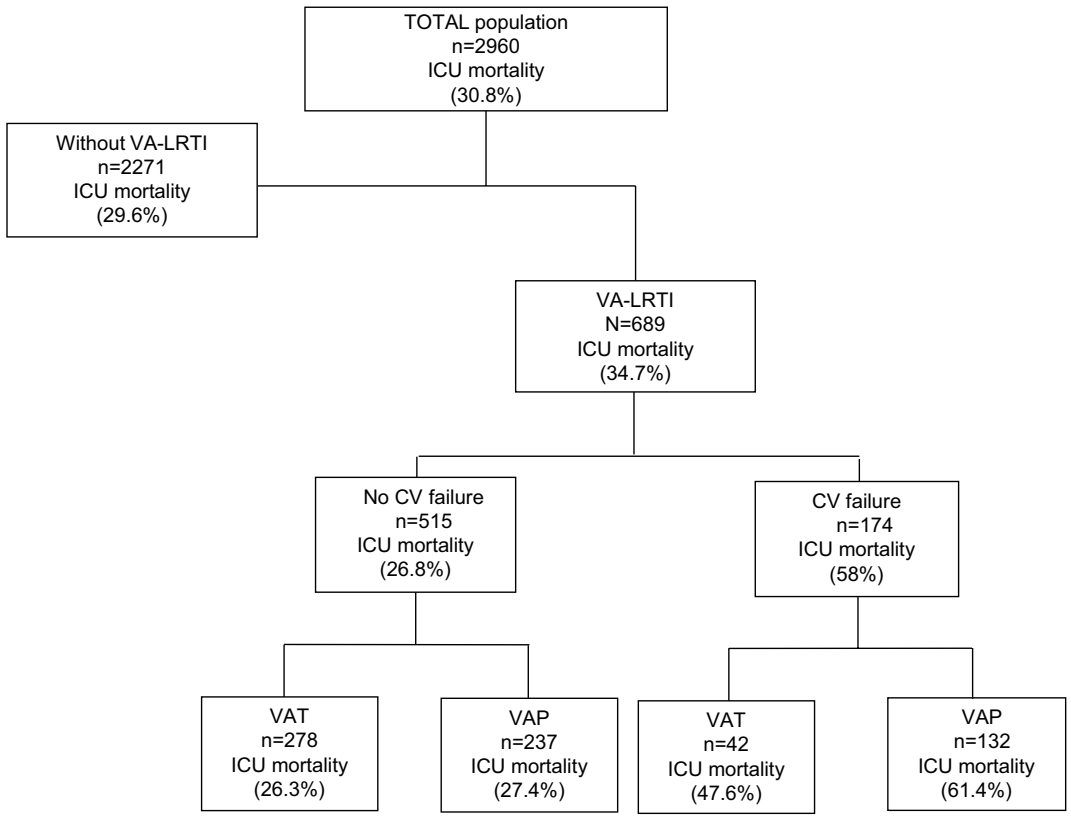

Fig. 1 Participant flow. *VA-LRTI* ventilator-associated lower respiratory tract infection, *CV* cardiovascular, *ICU* intensive care unit, *VAP* ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis

AF.15 packages. p values of < 0.05 were considered significant, unless stated otherwise.

Results

Among the initial cohort of 2960 patients, VA-LRTI occurred in 689 (23.2%). Among those with VA-LRTI, 174 (25.3%) presented cardiovascular failure at the day of diagnosis (Fig. 1). The group with VA-LRTI and cardiovascular failure were older, were more often medically admitted, had higher SAPS II scores on ICU admission, and presented with more organ failure (higher mSOFA) at the time of VA-LRTI diagnosis and more with immunosuppression. Previous antibiotic use was associated to a higher presence of MDR pathogens (63.6% vs. 36.4%; $p < 0.01$; OR 1.8; 95% CI 1.1–2.9). Length of stay in ICU was significantly longer in patients with cardiovascular failure than in those without (Table 1). Cardiovascular failure was more frequent in patients with VAP than in those with VAT (35.8% vs. 13.1%; $p < 0.001$; OR 3.6; 95% CI 2.5–5.4).

ICU mortality was 30.8% ($n = 912$) in the total population. Patients with VA-LRTI had a higher ICU mortality than those without (34.7% vs. 29.6%; $p < 0.01$; OR 1.2; 95% CI 1.1–1.5). Patients with cardiovascular failure had significantly higher ICU mortality than those without (58% vs. 26.8%; $p < 0.001$; OR 3.7; 95% CI 2.6–5.4). Both for VAP (61.4% vs. 27.4%; $p < 0.001$; OR 4.2; 95% CI 2.6–6.6) and for VAT (47.6% vs. 26.3%; $p < 0.01$; OR 2.5; 95% CI 1.3–4.9) cardiovascular failure was associated with higher ICU mortality. Patients who received appropriate antibiotic treatment showed a lower ICU mortality compared to those who received inappropriate antibiotic treatment (87.8% vs. 80.3%; $p < 0.01$; OR 0.5; 95% CI 0.3–0.8). The use of appropriate antibiotic treatment in the VAT group was associated with a significantly lower progression to VAP either in patients with (18.2% vs. 55.6%; $p < 0.03$; OR 0.1; 95% CI 0.1–0.8) or without cardiovascular failure (6% vs. 24.6%; $p < 0.0001$; OR 0.1; 95% CI 0.1–0.4). In Table 2 are displayed the risk factors analyzed for ICU mortality. Figure 2 shows the crude Kaplan–Meier survival curves of 90-day mortality according to the presence or absence of cardiovascular failure. Presence of cardiovascular failure was associated with increased ICU mortality ($p < 0.001$ with log-rank test).

Table 1 Patient characteristics by the presence or absence of cardiovascular failure

	No cardiovascular failure ($n=515$)	Cardiovascular failure ($n=174$)	p
Age (years), mean (SD)	58.6 (17.7)	61.67(17.2)	0.04
Male, *n* (%)	347 (67.4)	116 (66.7)	0.8
Admission type, *n* (%)			< 0.001
Medical	271 (52.6)	122 (70.1)	
Surgical	76 (14.8)	25 (14.4)	
Trauma	168 (32.6)	27 (15.5)	
SAPS II score, mean (SD)	47.5 (15.0)	54.9 (18.1)	< 0.001
mSOFA score, mean (SD)	6.2 (4.1)	11.3 (6.1)	< 0.001
Barthel score, mean (SD)	79.4 (33.4)	84.8 (32.2)	0.06
Medical conditions, *n* (%)			
COPD	88 (17.1)	37 (21.3)	0.2
CKD	46 (8.9)	23 (13.2)	0.1
Diabetes mellitus	100 (19.4)	35 (20.1)	0.8
Immunosuppression	30 (5.8)	25 (14.4)	< 0.001
Previous antibiotic use, *n* (%)	431 (87.4)	156 (91.8)	0.2
Appropriateness, *n* (%)	436 (84.7)	151 (86.8)	0.5
MDR, *n* (%)	293 (56.9)	128 (73.6)	< 0.001
VA-LRTI, *n* (%)			
VAP, *n* (%)	237 (46)	132 (75.9)	< 0.001
VAT, *n* (%)	278 (54)	42 (24.1)	< 0.001
ICU LOS (days), median (IQR)	20 (13–33)	28 (21–46)	0.2
Ventilator-free days, median (IQR)	41 (31–47)	37 (32–49)	0.1

CKD chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *IQR* interquartile range, *LOS* length of stay, *MDR* multi-drug resistant, *SAPS* Simplified Acute Physiology Score, *SD* standard deviation, *mSOFA* modified sequential organ assessment score, *MDR* multi-drug resistant, *VA-LRTI* ventilator-associated lower respiratory tract infection, *VAP* ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis

Multivariate analysis of the data of patients with and without cardiovascular failure is shown in Table 3. A propensity score analysis was conducted and found that appropriateness of antibiotic treatment was associated with a survival benefit only in patients without cardiovascular failure (Fig. 3). Figure 4 shows the predicted probabilities for ICU mortality according to the severity of the cardiovascular mSOFA score at the onset of VA-LRTI. When the propensity score analysis was conducted, only in patients without cardiovascular failure, the use of appropriate antibiotic treatment conferred a survival benefit for patients with VAP ($p < 0.01$; OR 0.4; 95% CI 0.3–0.7). The exclusion of eight patients who died within 48 h of the VA-LRTI diagnosis did not change the results (supplement Fig. 1).

Discussion

The main finding of this subanalysis of a multicenter observational cohort study on VA-LTRI was that appropriate antibiotic treatment was not associated with a survival benefit in patients with cardiovascular failure. Additionally, we found that in patients without cardiovascular failure, appropriate antibiotic treatment conferred a survival benefit for patients with VA-LRTI who had VAP.

When we interpret the results from this study, we found that whereas appropriate antibiotic treatment in more severe patients such as those with cardiovascular failure manifested by a cardiovascular mSOFA score equal to 4 did not show any association to a better ICU survival, but in patients without cardiovascular failure, it would be perhaps better to wait for the microbiological results and provide an appropriate directed treatment, instead of starting an inappropriate empirical treatment [24]. Based on our findings, two questions remain open based on the observational design of the study. On the one hand, whether the presence of cardiovascular failure is per se the driver of outcome and therewith VA-LRTI is not a driver of mortality, as the patients already have an unfavorable outcome. On the other hand, in patients without cardiovascular failure, whether the presence of VA-LRTI can be of influence on the main outcomes. The timing of antibiotic administration in patients with sepsis has been a seemingly constant matter of debate [25]. Early recognition of sepsis and administration of antibiotics is considered crucial for its treatment by the

Table 2 Risk factors for ICU mortality in patients with VA-LRTI

	Alive ($n=450$)	Death ($n=239$)	p
Age, mean (SD)	56.6 (17.7)	64.3 (15.9)	< 0.001
Male, *n* (%)	306 (62.9)	157 (61.5)	0.5
Admission type, *n* (%)			0.1
Medical	233 (62)	160 (67.9)	
Surgical	66 (19.6)	35 (15.7)	
Trauma	151 (18.5)	44 (16.4)	
SAPS II, mean (SD)	47.9 (17.9)	56.7 (18.5)	< 0.001
mSOFA score, mean (SD)	7.7(3.7)	9.1(3.8)	< 0.001
Barthel, mean (SD)	83.1 (30.8)	80.9 (30.4)	0.06
Medical conditions, *n* (%)			
COPD	74 (16.)	51 (21.3)	0.1
CKD	27 (6)	42 (17.6)	< 0.001
Diabetes	78 (17.3)	57 (23.8)	0.04
Immunosuppression	24 (5.3)	31 (13)	<0.001
Appropriateness, *n* (%)	395 (87.8)	192 (80.3)	< 0.01
MDR, *n* (%)	256 (56.9)	165 (69)	0.001
Cardiovascular failure, *n* (%)	73 (16,2)	101 (42.3)	< 0.01
VAP	223 (49.6)	146 (61.1)	< 0.001

CKD chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *MDR* multi-drug resistant, *SAPS* Simplified Acute Physiology Score, *SD* standard deviation, *mSOFA* modified sequential organ assessment score, *MDR* multi-drug resistant, *VA-LRTI* ventilator-associated lower respiratory tract infection, *VAP* ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis

Surviving Sepsis Campaign (SSC) guidelines [26]. There is no general disagreement that patients in the most severe end of the spectrum (septic shock) should receive prompt antibiotic therapy [27], but questions remain for those individuals who are not that sick [28–30]. As only ICU mortality has been the scope of this study, other patient-centered outcomes related to appropriate antibiotic treatment might be further studied. We have to acknowledge that other outcome variables, beside ICU mortality, have important implications in current clinical practice. When moving away from the fixed points of death, cost and quality of life outcomes, after both ICU and hospital discharge, are subject to increasingly difficult questions about their clinical relevance [31].

Ventilator-associated pneumonia prolongs the duration of mechanical ventilation and length of stay in the ICU, thereby contributing to the considerable economic burden associated with this condition [32]. The all-cause mortality rate for VAP is typically cited as being approximately 20–50% [33]. VAP has been associated with a higher crude ICU mortality rate. However, attributing mortality of VAP has been a matter of debate. Forel et al. found that in patients with ARDS whilst VAP increased crude ICU mortality, VAP was not found to be an independent risk factor for ICU mortality [34]. On the other hand, in a systematic review published by Melsen et al., the attributed mortality of VAP was reported to be 13%, with higher rates for surgical patients and patients with

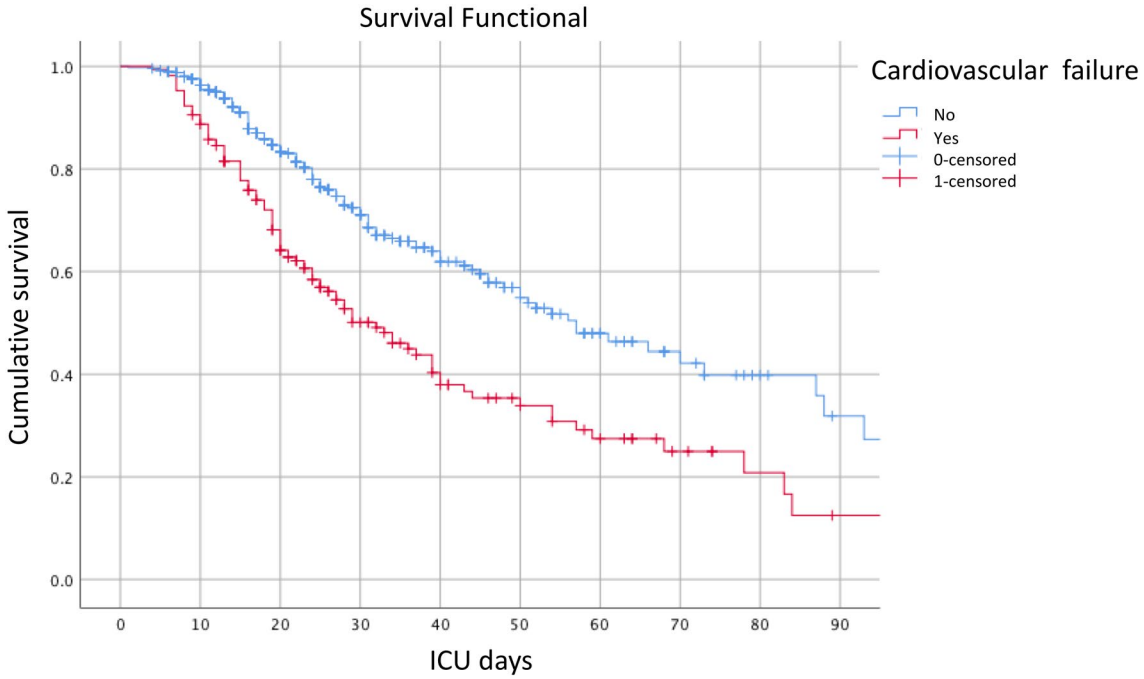

Fig. 2 Kaplan–Meier curve for ICU mortality according to the presence (red)/absence (blue) of cardiovascular failure ($p < 0.001$ with log-rank test). Abbreviations: ICU: intensive care unit

Table 3 Multi-variate analysis of risk factors associated with ICU mortality in patients with VA-LRTI, according to the presence or absence of cardiovascular failure

	Without cardiovascular failure		With cardiovascular failure	
	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
Age	1.0 (1.0–1.1)	< 0.005	1.0 (0.9–1.0)	0.07
SAPS II	1.0 (0.9–1.1)	0.08	1.1 (0.9–1.1)	0.4
Admission type				
Medical (reference)	1.0		1.0	
Surgical	0.9 (0.7–1.1)	0.5	1.1 (0.7–1.5)	0.3
Trauma	0.7 (0.5–0.9)	0.02	0.7 (0.5–1.3)	0.1
CKD	2.5 (1.2–4.8)	< 0.005	2.1 (0.7–5.9)	0.2
MDR	1.6 (1.0–2.5)	< 0.05	0.9 (0.4–1.9)	0.8
Appropriateness	0.5 (0.3–0.8)	< 0.005	0.6 (0.2–1.8)	0.3
VAP	1.5 (1.1–2.3)	0.01	1.7 (0.7–1.9)	0.7

A generalized estimating equation (GEE) model was fitted with a logit link, exchangeable correlation structure and non-robust standard errors. A country variable was included into the model to take into account potential country effects, however, it was not statistically significant ($p = 0.22$)

aOR adjusted odds ratio, *CI* confidence interval, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *MDR* multi-drug resistant, *OR* odds ratio, *SAPS* Simplified Acute Physiology Score, *VA-LRTI* ventilator-associated lower respiratory tract infection, *VAP* ventilator-associated pneumonia

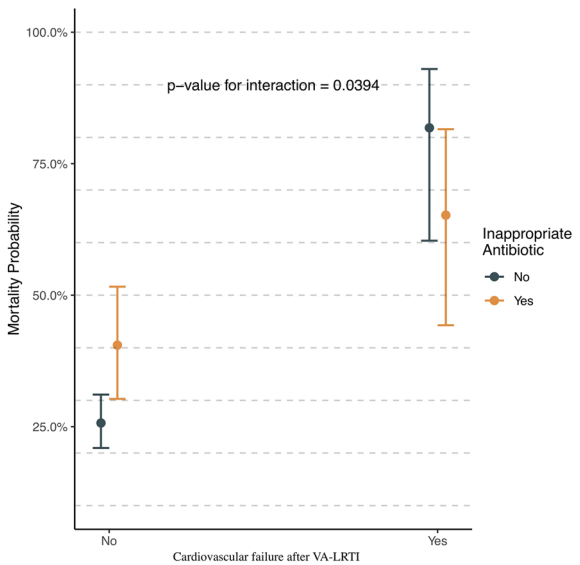

Fig. 3 Propensity score analysis to determine the association of appropriateness of antibiotic treatment and ICU mortality in patients with VA-LRTI. A total of 408 patients (102 that received inappropriate antibiotic treatment and 306 that received appropriate antibiotic treatment). OR for inappropriate antibiotic treatment 1.97 (95% CI 1.17–3.317, $p = 0.011$); OR for shock 13.00 (95% CI 4.26–36.70, $p < 0.001$)

a mid-range severity scores at admission [35]. In our research, although medical patients showed a significantly higher mortality in the multivariate analysis, this difference disappeared, when we adjusted for confounders in the multivariate analysis. In previous studies, we demonstrated that VAT was not an independent risk factor for mortality unlike VAP [3]. We also wanted to assess if appropriate antibiotic treatment might be associated with survival benefit in patients with VA-LRTI and cardiovascular failure [3, 14]. One could argue that VAT, per se, cannot be considered as a risk factor for cardiovascular failure, so we carefully evaluated every VAT episode to exclude potential confounders for cardiovascular failure manifested by a cardiovascular mSOFA. Therefore, based on our findings, we conclude that appropriate antibiotic treatment in the presence of cardiovascular failure did not affect mortality. This again opens the debate of whether treating VAT should be mandatory in every patient. In several observational studies, doing so offered no survival benefit. Currently, a randomized control trial (TAVeM2) is being conducted in France to determine if any VAT treatment can modify outcomes, specifically comparing the absence of therapy with short (3 days) and long (7 days) antibiotic courses [36].

We must acknowledge some limitations. First, this study was observational with an automatic selection of confounders and neither hospital mortality nor whether the presence of cardiovascular failure preceded or following the diagnosis of VA-LRTI was collected. VA-LRTI could be a complication of preceding cardiovascular failure with limited attributing mortality in itself, hence the lack of effect of antibiotics. Alternatively, however, cardiovascular failure could be the consequence of VA-LRTI and identify a subgroup with increased mortality attributing to VA-LRTI despite the prescription of appropriate antibiotic treatment. Whilst we report appropriateness of antibiotic treatment, timing of treatment, relevant dosage, and duration in compliance with guidelines were not collected and this represents a major limitation. The timing between diagnosis and treatment onset was not captured in the present database, precluding the use of current definitions of shock [37]. We therefore used cardiovascular failure as a surrogate of severity and we acknowledge that the presence of shock because of VAT is unlikely. Also, VAT is difficult to diagnose without computed tomography, yet only X-rays were used for diagnosis in either VAT or VAP. However, strength of this study is that it is the largest prospective observational study to-date in this area of research and in addition, gathered data from centers in different countries and continents without exclusion criteria and with strict and well-defined diagnostic criteria for VAP and VAT.

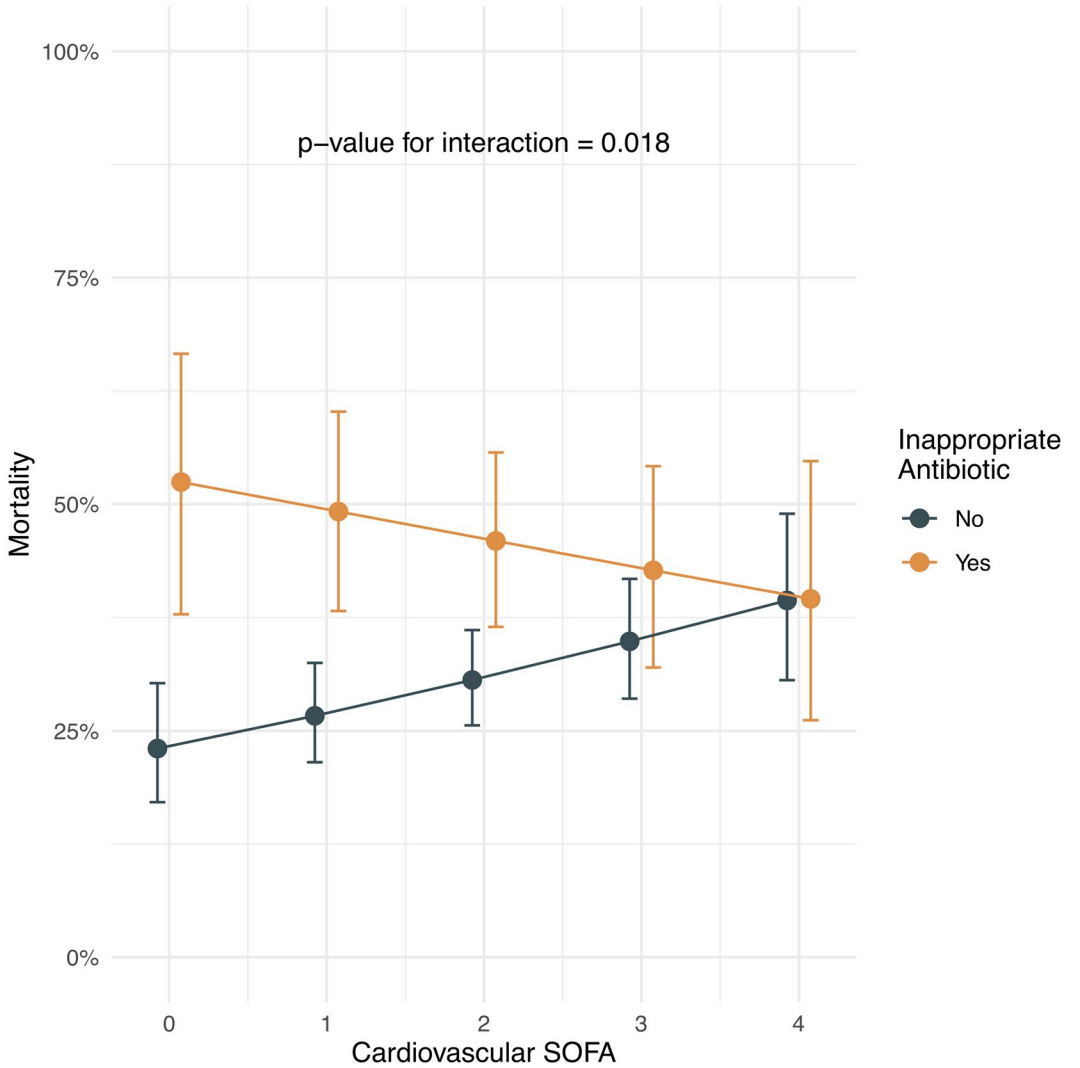

Fig. 4 Propensity score analysis to determine the association of the modifier cardiovascular mSOFA and ICU mortality according to appropriateness of antibiotic treatment in patients with VA-LRTI (propensity score with optimal matching)

Based on our research, in patients with VA-LRTI and cardiovascular failure, appropriate antibiotic treatment was not associated to a higher ICU survival. On the other hand, we found that in patients without cardiovascular failure, appropriate antibiotic treatment conferred a survival benefit for patients with VA-LRTI who only had VAP.

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