OBSERVATIONAL STUDY

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Determinants of Mortality for Ventilated Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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IMPORTANCE: Hospital-acquired pneumonia (HAP) is the most common hospital-acquired infection, accounting for 22% of all nosocomial infections. The available studies to date have not attempted to assess whether confounding factors may account for the observed difference in mortality for the two forms of nosocomial pneumonia associated with mechanical ventilation, namely ventilated HAP (vHAP) and ventilator-associated pneumonia (VAP).

OBJECTIVES: To determine if vHAP is an independent predictor of mortality among patients with nosocomial pneumonia.

DESIGN, SETTING, AND PARTICIPANTS: Single-center retrospective cohort study conducted at Barnes-Jewish Hospital, St. Louis, MO, between 2016 and 2019. Adult patients with a pneumonia discharge diagnosis were screened and patients diagnosed with vHAP and VAP were included. All patient data was extracted from the electronic health record.

MAIN OUTCOMES AND MEASURES: The primary outcome was 30-day all-cause mortality (ACM).

RESULTS: One thousand one-hundred twenty unique patient admissions were included (410 vHAP, 710 VAP). Thirty-day ACM was greater for patients with vHAP compared with VAP (37.1% vs 28.5%; $p = 0.003$). Logistic regression analysis identified vHAP (adjusted odds ratio [AOR], 1.77; 95% CI, 1.51–2.07), vasopressor use (AOR, 2.34; 95% CI, 1.94–2.82), Charlson Comorbidity Index (1-point increments) (AOR, 1.21; 95% CI, 1.18–1.24), total antibiotic treatment days (1-d increments) (AOR, 1.13; 95% CI, 1.11–1.14), and Acute Physiology and Chronic Health Evaluation II score (1-point increments) (AOR, 1.04; 95% CI, 1.03–1.06) as independent predictors of 30-day ACM. The most common bacterial pathogens identified as causes of vHAP and VAP were *Staphylococcus aureus*, *Enterobacterales* species, and *Pseudomonas aeruginosa*.

CONCLUSIONS AND RELEVANCE: In this single-center cohort study with low rates of initial inappropriate antibiotic therapy, vHAP had greater 30-day ACM compared with VAP after adjusting for potential confounding variables including disease severity and comorbidities. This finding suggests that clinical trials enrolling patients with vHAP need to account for this outcome difference in their trial design and data interpretation.

KEY WORDS: critical care; diagnosis; hospital-acquired pneumonia; intensive care; mortality; ventilator-associated pneumonia

Pneumonia is the most common infection treated within ICUs and carries significant mortality risk, especially for patients infected with antibiotic resistant bacteria (1). Hospital-acquired pneumonia (HAP) is the most common hospital-acquired infection, accounting for 22% of all nosocomial infections (2). Ventilator-associated pneumonia (VAP) is a specific form of HAP occurring in patients greater than 48 hours after intubation and the

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KEY POINTS

Question: Is ventilated hospital-acquired pneumonia (vHAP) associated with worse outcomes compared with ventilator-associated pneumonia (VAP)?

Findings: vHAP was associated with significantly greater antibiotic exposure, hospital length of stay, and 30-day all-cause mortality rates compared with VAP. This finding was confirmed when controlling for confounding variables including severity of illness.

Meanings: vHAP may have the greatest mortality risk among subtypes of nosocomial pneumonia. Efforts to minimize the risk of this infection should be prioritized.

initiation of mechanical ventilation, also carrying high risk of mortality (3). Recently, patients developing HAP and subsequently requiring intubation and mechanical ventilation have been categorized as having ventilated HAP (vHAP) (4). Several studies have suggested that vHAP has a greater crude mortality than other types of nosocomial pneumonia including VAP (5, 6).

The available studies to date have not attempted to assess whether confounding factors may account for the observed difference in mortality for the two forms of nosocomial pneumonia associated with mechanical ventilation, namely vHAP and VAP. Therefore, we carried out a retrospective cohort study with two main goals. Our first study goal was to assess the mortality risk in consecutive patients with vHAP and VAP cared for in a large referral center. Our second goal was to explore the risk factors for mortality in this patient cohort and to assess whether pneumonia type (vHAP vs VAP) was an independent predictor of hospital mortality.

METHODS

Study Design and Patient Population

This study was a retrospective cohort study of patients admitted to Barnes-Jewish Hospital, a 1,300-bed academic medical center in St. Louis, Missouri, from January 1, 2016, to December 31, 2019. All patient data was extracted from the electronic health record and the study was approved by the Washington University Institutional Review Board (No. 2018801189, Title "Outcomes associated with serious infections in hospitalized patients," initial approval January 31, 2018, most recent continuing review, March 22, 2022) without the need to obtain informed consent. We adhered to all Helsinki Declaration procedures during the conduct of this study.

Eligible adult patients with an *International Classification of Diseases*, 10th Revision, Clinical Modification discharge diagnosis code for pneumonia during the study period of interest were screened for inclusion (**Supplementary Appendix**, http://links.lww.com/CCX/B145). The cohort entry date was defined as the day a patient met all of the following criteria: 1) at least one sign of infection, including a WBC count greater than or equal to 11 or less than or equal to 4×10^9 cells/L, or temperature greater than or equal to 38 or less than or equal to 36°C; 2) new antibiotic orders; 3) chest radiograph order within ± 24 hours of criteria 1 and 2; and 4) criteria 1–3 had to occur greater than or equal to 48 hours after hospital admission. To further support the diagnosis of pneumonia, a random sample of patients had their chest radiographs reviewed by an investigator (M.H.K.) blinded to group allocation, which demonstrated greater than 95% agreement with the presence of radiographic infiltrates that could be consistent with pneumonia. Patients were defined as having vHAP if they were initiated on mechanical ventilation during the 48-hour window immediately after meeting cohort entry. Patients were categorized as having VAP if cohort entry occurred greater than or equal to 48 hours after the initiation and continuation of mechanical ventilation (7). Only the first eligible admission for a given patient was included. Patients were excluded if they met criteria for pneumonia during the first 48 hours of hospital admission, did not require mechanical ventilation, or were discharged or expired prior to day 3 of hospital admission.

All pharmacy-verified IV and oral antibiotic orders of interest were captured for each day of admission. Oral vancomycin, oral sulfamethoxazole/trimethoprim, and IV daptomycin orders were excluded. During the time of study, Barnes-Jewish Hospital used an antibiotic control program to help guide antimicrobial therapy for bacterial infections. The use of ceftolozane/tazobactam, ceftazidime/avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol, required an infectious diseases consultation to initiate

use. All other antibiotics could be ordered by any prescriber and did not require evaluation by any member of the antimicrobial stewardship team with the exception of ceftaroline which required evaluation within 72 hours of initiation. Each ICU and hospital ward had a clinical pharmacist who reviewed all antibiotic orders to ensure that dosing and interval of antibiotic administration was adequate for individual patients based on body size, renal function, and the resuscitation status of the patient. The duration of antibiotic treatment was defined as the number of days the patient was exposed to antibiotics during the 28 days following cohort entry. Initial inappropriate antibiotic treatment (IIAT) of vHAP and VAP was defined as receiving antibiotics that were not active in vitro against the culprit bacteria recovered. If the patient was culture-negative, they were deemed to have received appropriate antibiotic treatment.

The Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, modified to exclude the Glasgow Coma Scale score since this parameter was not documented in the electronic health record, was used to assess baseline severity of illness on ICU admission. The Charlson Comorbidity Index (CCI) was calculated using methods previously described to assess comorbidities at baseline (8). Orders for immunosuppressive medications were queried during the index admission and up to 30 days prior (Supplementary Appendix, http://links.lww.com/CCX/B145). Vasopressor orders queried included norepinephrine, vasopressin, and dobutamine.

Microbiologic data, including respiratory cultures, respiratory viral polymerase chain reaction tests, methicillin-resistant *Staphylococcus aureus* nasal culture swabs, and blood cultures were collected from days –1 to 3 of index pneumonia diagnosis. Respiratory cultures were divided into sputum-like specimens, which included sputum and tracheal aspirates, and cultures from bronchoscopy specimens, which included bronchoalveolar lavage (BAL), bronchial washings, and bronchial brushings. Respiratory samples identified as positive for a likely pathogen excluded specimens positive only for yeast, fungal structural elements, and/or clinically insignificant flora. Blood cultures identified as likely pathogens excluded results reported as coagulase-negative *Staphylococci*. Rapid molecular testing available during the study period included the BioFire Respiratory 2.1 Panel (BioFire Diagnostics, Salt Lake City, UT), which our laboratory has validated on the use of lower respiratory tract specimens, and the Verigene Gram-positive blood culture nucleic acid test (Nanosphere, Northbrook, IL). Results from these rapid molecular tests were updated in the chart without active intervention on behalf of the antimicrobial stewardship team. All in vitro testing was performed in the microbiology laboratory via Kirby-Bauer disk diffusion following the guidelines and the breakpoints established by the Clinical Laboratory and Standards Institute. All interpretations were made by trained microbiology technicians.

Outcomes

The primary outcome was 30-day all-cause mortality (ACM). Secondary outcomes included total hospital length of stay, ICU days, ventilator days, new vasopressor initiation, and development of acute kidney injury (AKI). AKI was defined using serum creatinine according to the Kidney Disease Improving Global Outcomes guidelines (9). Baseline serum creatinine was defined as the maximum creatinine value on day zero.

Statistical Analysis

Baseline characteristics are presented using descriptive statistics. Categorical variables were compared using the chi-square test. Continuous variables were assessed for normality and compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. The primary outcome of 30-day ACM was assessed using a log-rank test and Kaplan-Meier survival curves. To determine factors independently associated with the primary outcome, we employed logistic regression. The regression was a stepwise, backwards approach and all variables significant at the 0.15 level in univariate analysis, as well as pneumonia type (vHAP vs VAP) and factors known to influence mortality were entered into the model. Variables were assessed for co-linearity. We assessed goodness of fit with the Hosmer-Lemeshow test and R^2 values. Adjusted odds ratios (AORs) and 95% CIs are presented where appropriate. Significance was defined as a p value of less than 0.05. We did not carry out a sample size determination. Instead, we used a convenience sample size based on access to patients with vHAP and VAP at our institution during the study period.

All data were analyzed using IBM SPSS Statistics for Mac, version 28 (IBM Corp., Armonk, NY).

RESULTS

A total of 11,860 admissions from 9,717 unique patients were screened for inclusion (**Fig. 1**). Of these, 10,740 admissions were excluded. The most common reasons for exclusion were failure to meet pneumonia criteria, meeting pneumonia criteria within 48 hours of admission and having non-vHAP. The final cohort consisted of 1,120 specific patient admissions, of which 710 (63.4%) were identified as VAP and 410 (36.6%) as vHAP (Fig. 1). The median age was 61 years and 60% of patients were male. The median time to pneumonia diagnosis was 5 days.

Baseline characteristics are shown in **Table 1**. Patients with vHAP were significantly older and were more likely to be White. vHAP patients had a significantly greater comorbidity burden as indicated by higher CCI scores and higher occurrence rate of heart failure, peripheral vascular disease, chronic kidney disease, leukemia, receipt of a stem cell transplant or lung transplant, and to have received immunosuppressive therapy in the 30 days prior to admission. However, severity of illness on the day of diagnosis as indicated by APACHE II scores were significantly lower in patients with vHAP.

Patients with vHAP were significantly more likely to have positive blood cultures compared with patients with VAP (**Table 2**). vHAP patients were also significantly more like to have a BAL performed with specimens sent for culture. Table 2 shows that bacteria were identified in 32.4% of all patients in our study cohort with *S. aureus*, *Pseudomonas aeruginosa*, and *Enterobacterales* species predominating. Patient with vHAP were significantly less likely to have bacteria identified as well as the specific identification of *P. aeruginosa* and *Klebsiella* species compared with patients with VAP.

The most common initial antibiotics ordered for treatment of vHAP and VAP were vancomycin, cefepime, meropenem, and linezolid (**Supplementary Fig. 1**, http://links.lww.com/CCX/B145). Patients with vHAP were significantly more likely to receive meropenem, vancomycin, gentamicin, ertapenem, aztreonam, cefazolin, and metronidazole and were significantly less likely to receive azithromycin compared with patients with VAP. IIAT was low and similar for both groups (vHAP 5.1% vs VAP 5.2%; $p = 0.948$).

Primary and secondary outcomes are shown in **Table 3**. Overall, 30-day ACM was 31.6%. Patients with vHAP had statistically greater 30-day ACM and hospital mortality (Table 3). Kaplan-Meier curves demonstrated that patients with vHAP had lower

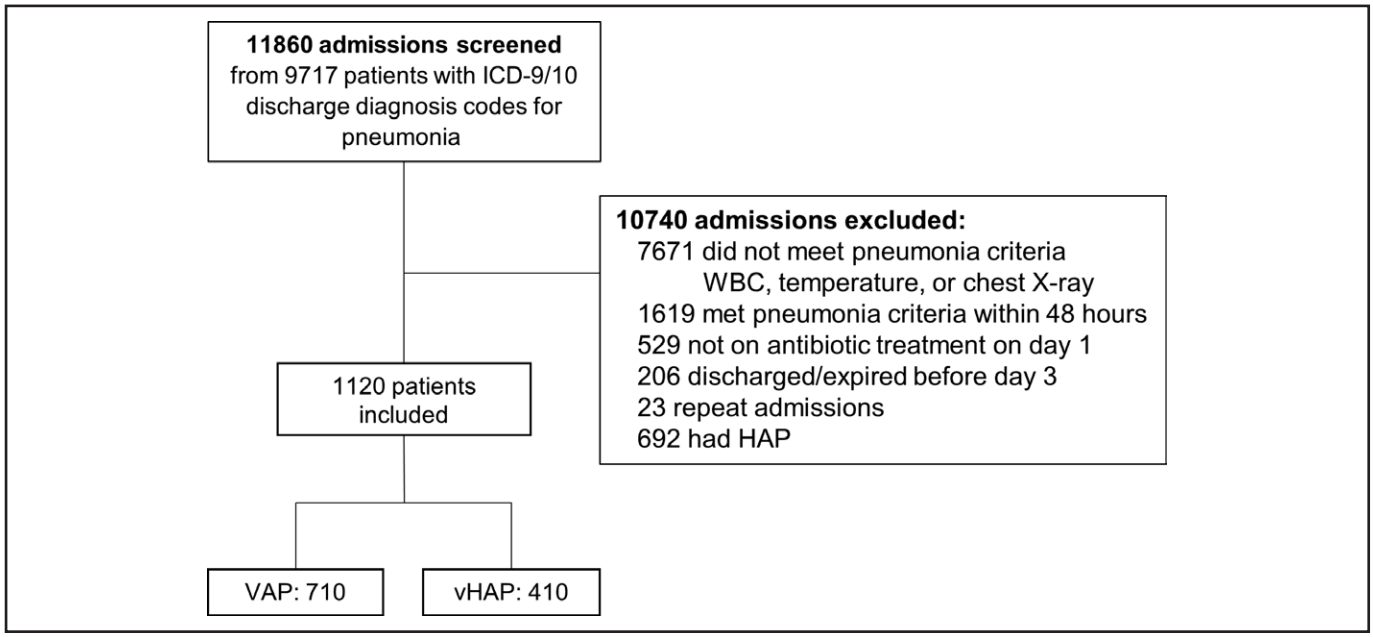

Figure 1. Study flow diagram. HAP = hospital-acquired pneumonia, ICD-9 = International Classification of Diseases, 9th Revision, ICD-10 = International Classification of Diseases, 10th Revision, VAP = ventilator-associated pneumonia, vHAP = ventilated hospital-acquired pneumonia.

TABLE 1.
Baseline Characteristics

Patient Characteristic	Total ($n = 1,120$)	Ventilated Hospital-Acquired Pneumonia ($n = 410$)	Ventilator-Associated Pneumonia ($n = 710$)	p
Age	61 (50–70)	63 (54–71)	60 (48–69)	< 0.001
Female	442 (39.5)	151 (36.8)	291 (41.0)	0.170
Race				0.003
White	783 (70.0)	311 (75.9)	472 (66.5)	
Black	284 (25.4)	78 (19.0)	206 (29.0)	
Other/unknown	53 (4.7)	21 (5.1)	31 (4.4)	
Body mass index	28 (23–34)	27 (23–33)	28 (24–34)	0.014
Acute Physiology and Chronic Health Evaluation II	14 (10–18)	11 (9–15)	15 (12–19)	< 0.001
Charlson Comorbidity Index 1 yr	4 (2–6)	4 (2–6)	3 (2–6)	< 0.001
Comorbidities				
Heart failure	513 (45.8)	213 (52.0)	300 (42.3)	0.002
Myocardial infarction	287 (25.6)	100 (24.4)	187 (26.3)	0.472
Stroke	254 (22.7)	86 (21.0)	168 (23.7)	0.301
Peripheral vascular disease	187 (16.7)	81 (19.8)	106 (14.9)	0.037
Chronic obstructive pulmonary disease	206 (18.4)	73 (17.8)	133 (18.7)	0.700
Liver disease	172 (15.4)	70 (17.1)	102 (14.4)	0.226
Chronic kidney disease	394 (35.2)	166 (40.5)	228 (32.1)	0.005
Diabetes	324 (28.9)	124 (30.2)	200 (28.2)	0.461
Dementia	43 (3.8)	15 (3.7)	28 (3.9)	0.811
HIV	14 (1.3)	6 (1.5)	8 (1.1)	0.625
Leukemia	59 (5.3)	33 (8.0)	26 (3.7)	0.002
Lymphoma	39 (3.5)	17 (4.1)	22 (3.1)	0.357
Cystic fibrosis	16 (1.4)	9 (2.2)	7 (1.0)	0.100
Transplant status				
Solid organ transplant	26 (2.3)	11 (2.7)	15 (2.1)	0.542
Lung transplant	31 (2.8)	11 (2.7)	20 (2.8)	0.895
Stem cell transplant	41 (3.7)	23 (5.6)	18 (2.5)	0.008
Immunosuppressive in prior 30 d	125 (11.2)	66 (16.1)	59 (8.3)	< 0.001
Days from admit to cohort entry	5 (3–9)	5 (3–11)	4 (2–8)	< 0.001

Results are shown as *n* (%) or median (interquartile range) unless otherwise indicated.

overall survival compared with patients with VAP (log-rank test = 0.004) (**Fig. 2**). Duration of mechanical ventilation was longer for patients with VAP.

Univariate analysis comparing 30-day survivors to nonsurvivors is shown in **Supplementary Table 1** (http://links.lww.com/CCX/B145). **Table 4** shows the results of the logistic regression analysis. After controlling for confounding variables, vHAP was found to be a significant predictor of 30-day ACM (AOR, 1.77; 95% CI, 1.51–2.07). Other identified independent predictors of 30-day ACM were vasopressor use (AOR, 2.34; 95% CI, 1.94–2.82), Charlson Comorbidity Index (1-point increments) (AOR, 1.21; 95% CI, 1.18–1.24), total antibiotic treatment days

TABLE 2.
Antibiotic and Culture Data

Microbiology	Total ($n = 1,120$)	Ventilated Hospital-Acquired Pneumonia ($n = 410$)	Ventilator-Associated Pneumonia ($n = 710$)	p
Blood culture obtained	838 (74.8)	317 (77.3)	521 (73.4)	0.144
Positive blood culture	62 (5.5)	30 (7.3)	32 (4.5)	0.048
Any respiratory culture obtained	765 (68.3)	269 (65.6)	496 (69.9)	0.141
Sputum, induced-sputum, and tracheal aspirates culture obtained	502 (44.8)	152 (37.1)	350 (49.3)	< 0.001
Bronchoalveolar lavage, bronchoscopic washing or brushings culture obtained	385 (34.4)	163 (40.0)	222 (31.3)	0.004
Respiratory culture positive[a]	432 (38.6)	126 (30.7)	306 (43.1)	< 0.001
Organism identified				
Bacteria	363 (32.4)	103 (25.1)	260 (36.6)	< 0.001
Yeast	179 (16.0)	57 (13.9)	122 (17.2)	0.149
Mold	18 (1.6)	7 (1.7)	11 (1.5)	0.839
Virus	94 (8.4)	36 (8.9)	58 (8.2)	0.722
Mycobacteria	2 (0.2)	2 (0.5)	0 (0.0)	0.630
Gram-positive bacteria				
Staphylococcus aureus	147 (13.1)	41 (10.0)	106 (15.0)	0.190
Methicillin-sensitive *S. aureus*	74 (6.6)	18 (4.4)	56 (7.9)	0.332
Methicillin-resistant *S. aureus*	73 (6.5)	23 (5.6)	50 (7.0)	0.332
Vancomycin-intermediate *S. aureus*	2 (0.2)	0 (0.0)	2 (0.3)	0.376
Streptococcus pneumoniae	14 (1.2)	2 (0.5)	12 (1.7)	0.081
Streptococcus agalactiae	5 (0.4)	2 (0.5)	3 (0.4)	0.875
Nonfermenting Gram-negative bacteria				
Pseudomonas aeruginosa	59 (5.3)	9 (2.1)	50 (7.0)	< 0.001
Acinetobacter species	12 (1.1)	6 (1.5)	6 (0.8)	0.333
Burkholderia species	4 (0.4)	0 (0.0)	4 (0.6)	0.128
Stenotrophomonas maltophilia	20 (1.8)	4 (1.0)	16 (2.2)	0.120
Enterobacterales				
Klebsiella species	29 (2.6)	4 (1.0)	25 (3.5)	0.010
Enterobacter species	36 (3.2)	11 (2.7)	25 (3.5)	0.440
Escherichia coli	31 (2.8)	13 (3.2)	18 (2.5)	0.532
Proteus species	6 (0.5)	1 (0.2)	5 (0.7)	0.309
Serratia marcescens	22 (2.0)	6 (1.5)	16 (2.2)	0.359
Other Gram-negative bacteria				
Haemophilus species	25 (2.2)	8 (2.0)	17 (2.4)	0.629
Moraxella catarrhalis	7 (0.6)	2 (0.5)	5 (0.7)	0.658
Polymicrobial	61 (5.4)	14 (3.4)	47 (6.6)	0.028
Total antibiotic days (cohort entry to day 28)	11 (7–17)	12 (8–18)	11 (7–16)	0.029
Inappropriate initial antibiotic treatment	58 (5.2)	21 (5.1)	37 (5.2)	0.948

[a]Excludes normal oral flora, insignificant bacterial growth, and isolated finding of yeast.
Results are shown as *n* (%) or median (interquartile range) unless otherwise indicated.

TABLE 3.
Primary and Secondary Outcomes

Outcomes	Total ($n = 1,120$)	Ventilated Hospital-Acquired Pneumonia ($n = 410$)	Ventilator-Associated Pneumonia ($n = 710$)	p
Hospital mortality	338 (30.2)	145 (35.3)	193 (27.2)	0.004
30-d all-cause mortality	354 (31.6)	152 (37.1)	202 (28.5)	0.003
Vasopressors	179 (16.0)	78 (19.0)	101 (14.2)	0.035
ICU days	14 (8–23)	14 (8–23)	15 (9–24)	0.018
Hospital days	22 (14–37)	25 (15–40)	21 (13–35)	0.002
Pneumonia readmission[a]	25 (2.2)	15 (3.7)	25 (3.5)	0.900
Readmission any cause[a]	207 (18.5)	72 (17.6)	135 (19.0)	0.546
Ventilator days	10 (6–18)	8 (4–8)	12 (7–19)	< 0.001
Acute kidney injury	148 (13.2)	57 (13.9)	91 (12.8)	0.605

[a]Thirty-day readmission.
Results are shown as *n* (%) or median (interquartile range) unless otherwise indicated.

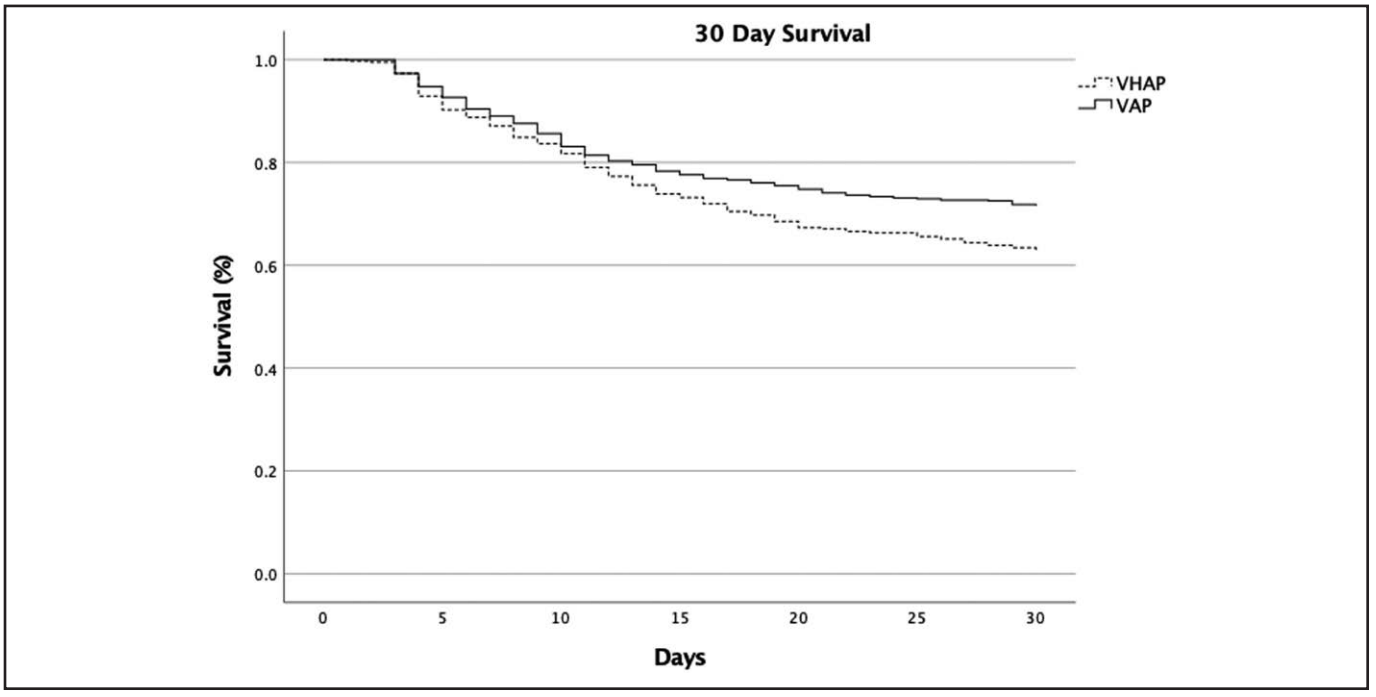

Figure 2. Kaplan-Meier survival curves for 30-d all-cause mortality. Log-rank test: $p = 0.004$. VAP = ventilator-associated pneumonia, vHAP = ventilated hospital-acquired pneumonia.

(1-d increments) (AOR, 1.13; 95% CI, 1.11–1.14), and APACHE II score (1-point increments) (AOR, 1.04; 95% CI, 1.03–1.06).

DISCUSSION

In this study of 1,120 patients with vHAP and VAP, patients developing vHAP were found to have significantly greater 30-day ACM by univariate analysis. Multivariate logistic regression analysis identified vHAP to be an independent predictor of 30-day ACM. Multivariate analysis also identified the use of vasopressors, which occurred more often in patients with vHAP, to be an independent predictor of 30-day ACM.

We previously demonstrated in a case-control study that patients with non-vHAP occurring on non-ICU

TABLE 4.
Logistic Regression Analysis: Predictors of 30-Day All-Cause Mortality

Variable	Hazard Ratio (95% CI)	*p*
Use of vasopressors	2.34 (1.94–2.82)	< 0.001
Ventilated hospital-acquired pneumonia	1.77 (1.51–2.07)	< 0.001
Charlson comorbidity score (1-point increments)	1.21 (1.18–1.24)	< 0.001
Total antibiotic days (1-d increments)	1.13 (1.11–1.14)	< 0.001
Acute Physiology and Chronic Health Evaluation II score [a] (1-point increments)	1.04 (1.03–1.06)	0.001

[a]Acute Physiology and Chronic Health Evaluation II score does not include the Glasgow Coma Scale Assessment/Hosmer-Lemeshow test = 0.378.

floors were more likely to die, to require intensive care or mechanical ventilation, and to have a longer hospital length of stay compared with similar hospitalized patients not developing HAP (10). Furthermore, the development of HAP and subsequent need for mechanical ventilation were identified as independent determinants of hospital mortality. This observation supported the occurrence of HAP as a key outcome determinant among hospitalized patients. More recently, Zilberberg et al (6) used the Premier database of acute care hospitals to compare the outcomes of patients with various forms of nosocomial pneumonia including vHAP and VAP. These investigators found that vHAP was associated with the highest comorbidity burden and VAP with the lowest. Similarly, hospital mortality was highest among patients with vHAP (29.2%) and lowest in non-vHAP (11.7%), with VAP being in-between (21.3%) (6). These findings were consistent with other observational nosocomial pneumonia treatment studies identifying vHAP as having the greatest mortality risk among subtypes of nosocomial pneumonia (5).

Our study is unique in assessing the risk of 30-day ACM between patients with vHAP and VAP while controlling for potential confounding factors such as disease severity and comorbid conditions. Our cohort, coming from a single center with longstanding treatment protocols for nosocomial pneumonia, also minimized antimicrobial practice variability and the administration of IIAT (11–13). Other strengths of our study include that it is a contemporary cohort prior to the COVID-19 pandemic, which reflects current clinical practices. We screened patients using strict enrollment criteria for nosocomial pneumonia, notably excluding those who met these criteria too early in their hospital course. We also were able to collect and control for many confounding variables, including disease severity, comorbidities, and antibiotic appropriateness and duration utilizing a multivariable regression analysis.

Our study also has limitations. First, being a retrospective analysis we are limited in identifying all potential confounding variables that might have influenced 30-day ACM. For example, delays in the diagnosis of HAP on non-ICU hospital floors, among patients subsequently requiring mechanical ventilation and the corresponding delay in the administration of appropriate antibiotic therapy, may account for the worse outcomes observed in patients with vHAP. Several studies have shown that delays in the administration of appropriate antibiotic therapy for patients with nosocomial pneumonia can result in greater mortality (14, 15). Our observation that vHAP patients had a greater duration of time separating their pneumonia diagnosis from the time of hospital admission compared with patients with VAP may support this as a possible explanation for the mortality difference observed. Second, this was a single center study limiting the overall generalizability of our observations. Additionally, as a single-center retrospective review, this study is subject to selection bias. Third, despite accounting for many potential confounding variables and conducting a multivariable regression analysis, there may have also been additional unmeasured confounders that could have influenced the nature of the results. Pneumonia necessitating mechanical ventilation (vHAP) versus pneumonia complicating mechanical ventilation (VAP) could indicate more severe lung injury in the former, which we did not capture objectively, and could have factored into the result we observed. We also did not assess the duration of mechanical ventilation after the onset of VAP as a comparator to the vHAP group.

Another limitation of our study is that chest radiographs were not confirmed to have a new infiltrate in all patients. While radiographic evidence can certainly support the diagnosis of vHAP and VAP, pneumonia remains a clinical diagnosis. In our experience, many critically ill patients receive treatment for nosocomial pneumonia in the absence of radiographic findings. Additionally, all admissions screened for inclusion in this study had an *International Classification of Diseases* discharge diagnosis code for pneumonia. Thus, we believe this cohort is reflective of clinical practice and thus generalizable to other institutions with similar practices. Last, we cannot exclude the possibility that some of our patients with bacteremia had an alternative source of infection (e.g., catheter-associated bloodstream infection) that could have contributed to their mortality.

Nosocomial pneumonia remains a pressing public health problem and has increased in overall prevalence during the COVID-19 pandemic (16). Increasingly, patients with vHAP are being included in clinical trials of novel therapies for nosocomial pneumonia (17, 18). Given the findings from our study, it will be important for future trials of novel nosocomial pneumonia treatments to account for patients with vHAP entered into their studies.

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