Identification of Factors Affecting Mortality in Late-Onset Ventilator-Associated Pneumonia

Aziz Ahmad Hamidi, Serhat Kescioglu

ABSTRACT

Objective: Pneumonia that develops 48 hours after intubation has been defined as ventilator-associated pneumonia (VAP) in patients hospitalized in the intensive care unit (ICU). Late-onset VAP (LO-VAP) is described as pneumonia that occurs within or after the 5th day of mechanical ventilation. We aimed to determine the factors that affect the mortality and survival in patients with LO-VAP.

Materials and Methods: We retrospectively reviewed the hospital records of adult patients (>18 years) who developed LO-VAP in the training and research hospital between January 2014 and June 2018. We compared the demographic findings and laboratory characteristics of the survivors and deaths on the 28-day mortality.

Results: The mean age of 231 (90 female and 141 male) patients with LO-VAP was 73.43±14.06 years. As a result of multivariate logistic regression analysis, we determined that advanced age (p=0.023; 95% confidence interval [CI]: 1.003–1.047) and unconsciousness (p=0.001; 95% CI: 1.674–6.547) were the independent factors affecting mortality. However, parenteral nutrition (PN) (p=0.027; 95% CI: 0.263–0.923) and tracheostomy (p=0.001; 95% CI: 0.112–0.545) were the independent factors supporting survival. We found that acute physiology and chronic health evaluation II score, presence of bacteremia, and enteral nutrition did not have a significant effect on mortality.

Conclusion: Use of tracheostomy and PN in patients with LO-VAP has a positive effect on survival. Our study also points out that mortality can be high in patients with advanced age and unconsciousness.

Keywords: Hospital-acquired pneumonia, hospital infections, hospital mortality, ventilator-associated pneumonia

Introduction

Hospital-acquired infections increase the mortality of patients. In addition, they also increase the length and cost of hospital stays. Infections that develop in the intensive care unit (ICU) are 20% of all hospital-acquired infections [1]. Infectious disease is shown to be an independent mortality factor for patients hospitalized in ICU [2]. Pneumonia that is developed 48 hours after intubation in patients who received mechanical ventilation was defined as ventilator-associated pneumonia (VAP). Pneumonia developed in the first 4 days after intubation is defined as early-onset VAP (EO-VAP), whereas pneumonia developed after that time is defined as late-onset VAP (LO-VAP) [3]. VAP develops in 8%-28% of the patients on mechanical ventilation. The mortality rate in this infection varies between 24% and 50%. In cases where high-risk microorganisms are involved, this ratio can reach up to 76% [1]. Bacteremia, the high score of acute physiology and chronic health evaluation (APACHE), acute respiratory distress syndrome, multidrug-resistant bacteria, underlying severe disease, cavitary and multilobar cavitary, rapidly progressive lung infiltrations, and delay in appropriate antibiotic initiation are factors that increase mortality in patients with VAP [4–8].

The pathogenesis of EO-VAP is different from that of LO-VAP. Multidrug-resistant microorganisms were found to be more frequent in LO-VAP cases [9]. Therefore, it is necessary to determine the factors affecting the mortality by examining the EO-VAP and LO-VAP cases in separate studies. In this study, we aimed to determine the factors affecting mortality only in LO-VAP cases.

Cite this article as: *Hamidi AA, Kescioglu S. Identification of Factors Affecting Mortality in Late-Onset Ventilator-Associated Pneumonia. Eurasian J Med 2020; 52(3): 254-8.*

Department of Infection Diseases and Clinical Microbiology, Karabuk University School of Medicine, Karabuk University Training and Research Hospital, Sirinevler, Karabuk

Received: January 14, 2020
Accepted: March 13, 2020

Correspondence to: Aziz Ahmad Hamidi
E-mail: azizahmadhamidi@gmail.com

DOI 10.5152/eurasianjmed.2020.20005

Materials and Methods

We started working after the approval of Karabuk Medical Faculty Clinical Research Ethics Committee, Karabuk University, dated August 03, 2018 and numbered 77192459-050.99-E.3706. We retrospectively analyzed the hospital records of adult patients (>18 years) who developed VAP in the educational and research hospital's ICU between January 2014 and June 2018. For the diagnosis of VAP in a patient who received mechanical ventilation for at least 48 hours, we used the presence of newly developed or persistent infiltration in lung radiography and the presence of the following parameters [10]: (i) fever (≥38.5°C) or hypothermia (<36.5°C), (ii) Purulent tracheal secretions, and (iii) Leukocytosis (>109 cells/L) or leukopenia (<4×108 cells/L). Semiquantitative endotracheal aspirate (ETA) culture was evaluated to determine the causative microorganism. We defined secondary bacteremia in cases where the same bacteria were produced in the blood and ETA cultures. Patients who had VAP diagnostic criteria without causative agents in ETA culture were accepted as VAP. Pneumonia, which occurs on the 5th day and later after mechanical ventilation, was identified as LO-VAP. We included only the first VAP attack for each patient in our study. Patients' age; gender; underlying disease; ICU; parenteral nutrition (PN); enteral nutrition (EN); central venous catheter; peripheral venous catheter; peripheral artery catheter; urinary catheter; use of immunosuppression, blood transfusion, and hemodialysis; and causative agent were recorded in the prepared electronic medium. We evaluated the patients who were not conscious without any sedative medication as "unconscious." We calculated the 28-day mortality attributed to the infection of the 28-day survival time from the first infection attack. The duration of mechanical ventilation when VAP was diagnosed was identified as the duration of intubation. We calculated the APACHE II score by taking the clinical and laboratory findings on the day of VAP diagnosis. The cases were divided into 2 groups—surgical and internal ICU hospitalization—according to the diagnosis, where we defined coronary ICU as internal ICU and cardiovascular surgery ICU as surgical ICU.

Main Points

- PN and tracheostomy have a positive effect on survival in late-onset VAP cases.
- Advanced age and unconsciousness are independent risk factors for mortality.
- Acinetobacter baumannii was the most common agent.

We excluded patients with multiple microorganisms growing in the ETA culture, patients with <18 years of age, patients developing the first VAP episode during the first 4 days after mechanical ventilation, patients that did not meet the VAP diagnostic criteria despite the growth of microorganisms in the ETA culture, and patients with missing data in the hospital records from the study.

Statistical Analysis

We performed the statistical analysis of the data using the IBM Statistics Version 24 program (IBM SPSS Corp.; Armonk, NY, USA). Mann-Whitney U test was used to compare continuous data between the 2 groups. The effect of the variables on survival was assessed by single logistic regression analysis and multiple logistic regression analysis (using the forward LR method) with the model formed by variables that were significantly effective in single logistic regression. P<0.05 was considered to be statistically significant.

Results

We included 231 patients (90 female and 141 male) with LO-VAP who met the study criteria in the study. The mean age of these patients was 73.43±14.09 years. The demographic and clinical characteristics of the surviving and dying patients were compared (Table 1). As a result of univariate logistic regression analysis (Table 2), age, APACHE II score, unconsciousness, PN, and tracheostomy had an effect on the mortality (p-value 0.008, 0.01, 0.01, 0.02, and <0.001, respectively). The effects of other factors on mortality were not statistically significant (p>0.05). In the multivariate logistic regression analysis for these 5 factors, the effect of age, consciousness, PN, and tracheostomy factors were found to be statistically significant (Table 3). The effect of APACHE II score on mortality was not statistically significant (p>0.05). Advanced age (p=0.023; 95% confidence interval [CI]: 1.003–1.047) and unconsciousness (p=0.001; 95% CI: 1.674–6.547) were two independent factors that increased mortality. However, PN

Table 1. Comparison of characteristics of surviving and dying cases

Characteristics	Total (%) (n=231)	Survivors (%) (n=85)	Deaths (%) (n=146)	p
Age (mean)	73.43±14.06	69.86±16.04	75.51±12.36	0.008
Gender (female/male)	61/39	43.5/56.5	36.3/53	0.277
Intensive care unit (surgical/internal)	148/83	61/24	87/59	0.063
*APACHE II (mean)	20.84±4.67	19.93±5.27	21.38±4.21	0.010
Duration of intubation (days)	20.65±16.02	19.59±14.55	21.27±16.83	0.567
Bacteremia	27.2	25	28.5	0.570
Cerebrovascular event	27.3	27.1	27.4	0.956
Diabetes mellitus	15.2	12.9	16.4	0.475
Hypertension	27.7	24.7	29.5	0.437
Unconsciousness	72.4	64.7	79.9	0.011
Enteral nutrition	58	65.5	69.4	0.536
Immunosuppression	31	32.9	29.9	0.626
Peripheral artery catheter	96.1	95.3	96.5	0.650
Peripheral venous catheter	99.1	98.8	99.3	1.000
Central venous catheter	94.3	94.1	94.4	1.000
Parenteral nutrition	58.8	68.2	53.1	0.025
Blood transfusion	52.8	49.4	54.9	0.425
Urinary catheter	100	100	100	-
Tracheostomy	16.2	28.2	9	0.000
Nasogastric tube	69.9	63.5	73.6	0.108
Hemodialysis	13.6	10.6	15.4	0.307
Acinetobacter baumannii	39	35.3	41.1	0.383
Pseudomonas aeruginosa	22.5	20	24	0.578
Non-fermentative bacteria	61.5	55.3	65.1	0.468

*Acute physiology and chronic health evaluation

Table 2. Univariate logistic regression analysis for variables thought to be effective on mortality

Factors	B	Sig.	Exp(B)	95% C.I. for EXP(B)	
Age	0.029	0.004	1.029	1.009	1.050
Gender	0.302	0.278	1.353	0.784	2.334
*APACHE II	0.069	0.024	1.071	1.009	1.137
Duration of intubation	0.007	0.442	1.007	0.989	1.025
Bacteremia	0.177	0.570	1.194	0.647	2.203
Cerebrovascular event	0.017	0.956	1.017	0.558	1.855
Diabetes Mellitus	0.280	0.476	1.323	0.613	2.858
Hypertension	0.241	0.437	1.272	0.693	2.337
Unconsciousness	0.772	0.012	2.163	1.183	3.954
Enteral nutrition	0.181	0.536	1.198	0.676	2.125
Immunosuppression	-0.143	0.626	0.867	0.487	1.542
Peripheral artery catheter	0.310	0.651	1.363	0.356	5.221
Peripheral venous catheter	0.518	0.715	1.679	0.104	27.191
Central venous catheter	0.053	0.928	1.055	0.334	3.334
Parenteral nutrition	-0.639	0.026	0.528	0.301	0.927
Blood transfusion	0.219	0.425	1.244	0.727	2.129
Tracheostomy	-1.377	0.000	0.252	0.120	0.529
Nasogastric tube	0.471	0.109	1.601	0.900	2.850
Hemodialysis	0.429	0.309	1.535	0.672	3.510
Acinetobacter baumannii	0.246	0.384	1.279	0.735	2.225

*APACHE: Acute physiology and chronic health evaluation; C.I.: Confidence interval

Table 3. Multivariate logistic regression analysis for variables found significant in univariate regression analysis

Factors	B	Sig.	Exp(B)	95% C.I. for EXP(B)	
Age	0.025	0.023	1.025	1.003	1.047
Unconsciousness	1.197	0.001	3.310	1.674	6.547
Parenteral nutrition	-0.707	0.027	0.493	0.263	0.923
Tracheostomy	-1.397	0.001	0.247	0.112	0.545
Constant	-1.489	0.093	0.226		

(p=0.027; 95% CI: 0.263-0.923) and tracheostomy (p=0.001; 95% CI: 0.112-0.545) were the factors that affected survival. In terms of invasive device use, 100% of patients had urinary tract catheter, 99.1% had peripheral venous catheter, and 94.3% had central venous catheter. In total, mean intubation time was 20.65 (±16.02) days, and there was no statistically significant difference between the surviving and the dying groups. *Acinetobacter baumannii* was present in 39% (90) of patients, and *Pseudomonas aeruginosa* was the cause of VAP in 22.5% (52) patients. There was no statistically significant difference between the surviving and dying groups in terms of *A. baumannii* and *P. aeruginosa*. In addition, *Klebsiella pneumoniae* in 15, *Escherichia coli* in 9, *Staphylococcus aureus* in 9, *Enterobacter cloacae* in 6, *Enterococcus faecium* in 4, *Serratia marcescens* in 4, *Streptococcus pneumoniae* in 1 patient, and *Stenotrophomonas maltophila* in 1 patient were detected. No microorganisms were detected in 37% of the patients.

Discussion

In this study, age and consciousness were found to be the independent factors increasing mortality. Besides, tracheostomy and PN were found to be the decisive factors for survival. Previous studies have shown that older age is a risk factor for VAP development [1, 11]. However, a multicenter prospective cohort study showed that older age did not affect the frequency of VAP but was associated with mortality [12]. Another study found that advanced age was the only independent factor associated with mortality in patients with VAP [13]. Similarly, we found that the mean age of the patients was high (73.43±14.06), and advanced age was an independent mortality factor in our study.

The aspiration of contaminated gastric and oropharyngeal secretions plays an essential role in the introduction of bacteria to the lower respiratory tract in patients receiving mechanical ventilation support [14]. The relation between EN, aspiration, and VAP was investigated in previous studies. EN was found to be a risk factor for nosocomial pneumonia in patients on mechanical ventilation [15]. Subsequent studies showed no difference in gastric and oropharyngeal microaspiration rate, VAP development rate, and mortality rate in patients receiving PN and EN [16, 17]. In our study, no significant difference was found between the surviving and dying groups in terms of EN. However, the presence of PN was an effective independent factor in the survival of patients with VAP.

Early tracheostomy has been shown to lead to a reduction in the incidence and mortality rates of hospital-acquired pneumonia compared with late tracheostomy and no tracheostomy [18, 19]. In another study, no tracheostomy was shown to be a long-term predictor of mortality for VAP [20]. Similarly, in our study, the rate of tracheostomy was higher in survivors than in those who died. Besides, the presence of tracheostomy was an effective independent factor for survival.

Unconsciousness causes prolonged ventilation time and constitutes a risk factor for VAP development [21, 22]. In addition, it has been shown in a study that unconsciousness is an independent risk factor for mortality in patients with VAP [23]. Similarly, in our study, as a result of multivariate analysis, unconsciousness was found to be a mortality factor. Unconsciousness indicates the severity of infection and sepsis. This explains the higher rate of unconsciousness in the dying group.

The APACHE II score was found to be a prognostic factor for mortality in previous studies [24, 25]. In a study in which prognostic risk factors for VAP were investigated using univariate analysis, the APACHE II score was found to be statistically different between those who died and survived. However, it was not found to be an independent risk factor for mortality in multivariate logistic regression analysis [9]. Similarly, in our study, the effect of APACHE II score on mortality was not statistically significant in multivariate logistic regression analysis (p>0.05).

There was no difference between the gender of patients and VAP development in many studies [20, 23]. However there is a study which the

male gender is detected significantly more in the late-onset nosocomial pneumnia compared to patients with early-onset nosocomial pneumonia [26]. In our study, 61% of the patients were male, and there was no relationship between mortality and gender. Bacteremia, prolonged intubation, renal insufficiency, and hemodialysis are the factors that increase the risk of mortality in hospital-acquired pneumonia [20, 27]. In another study, however, the intubation duration before VAP and hemodialysis were similar in surviving and dying patients [28]. In our study, no statistically significant difference was found between the surviving and dying groups in terms of hemodialysis, bacteremia, and intubation period.

Toufen et al. [2] found higher mortality rates (26.1% versus 35.2%) in patients with internal ICU compared with surgical ICU, whereas we did not found a significant difference in terms of mortality rate between the two ICUs.

In a meta-analysis, the growth of non-fermentative gram-negative bacteria and *A. baumannii* was found to be associated with high mortality [29]. Non-fermentative bacteria (39% *A. baumannii* and 22.5% *P. aeruginosa*) were the causative agents in 61.5% of patients in our study. However, there was no statistically significant difference in the distribution of microorganisms between the surviving and dying groups. Since all the cases were LO-VAP, the presence of resistant microorganisms in both the groups explains this situation. In a recent comprehensive study, *A. baumannii* was found to be the most frequent VAP agent in Turkey [30]. The distribution of causative microorganisms in our study is consistent with the literature.

Many studies have shown that initial antibiotic therapy is an essential factor affecting mortality [4–6]. However, our study does not include the rate of appropriate initial antibiotic therapy. This is among the limitations of our study. Furthermore, the fact that our study was retrospective, the resistance profile of the causative microorganisms, and no investigation of the treatment results are also the limitations of our study.

In conclusion, the data in our study showed that advanced age and unconsciousness were independent factors affecting the 28-day mortality. However, the two factors that were affecting the survival are PN and tracheostomy. Bacteremia, EN, and APACHE II did not affect the 28-day mortality. In this study, we recommend early tracheostomy and PN in patients with VAP. We also note that mortality can be high in patients with advanced age and who are unconsciousness for any reason.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Karabuk University School of Medicine (03.08.2018/77192459-050.99-E.3706).

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.A.H., S.K.; Design - A.A.H., S.K.; Supervision - A.A.H., S.K.; Resources - A.A.H.; Materials - A.A.H.; Data Collection and/or Processing - A.A.H., S.K.; Analysis and/or Interpretation - A.A.H., S.K.; Literature Search - A.A.H., S.K.; Writing Manuscript - A.A.H., S.K.; Critical Review - A.A.H., S.K.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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