Dicle Tıp Dergisi / Dicle Med J (2022) 49 (4) : 635-644

www.diclemedj.org

Original Article / Özgün Araştırma

Risk Factors for 7-Day and 21-Day Mortality in Patients with Ventilator-Associated Pneumonia Caused by Gram-Negative Multidrug Resistant Bacteria

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Received:03.04.2022; Revised:04.11.2022; Accepted: 07.11.2022

Abstract

Objective: Incidence of ventilator-associated pneumonia, caused by gram-negative multidrug resistant bacteria, is on the increase and early mortality rate is high.

We aimed to investigate the effects of aging, comorbidities, high Charlson comobidity index score, high Acute Physiology and Chronic Health Evaluation II score, leukocytosis, high C-reactive protein level, inappropriate empirical antibiotic therapy and antibiotic resistance on mortality in ventilator-associated pneumonia caused by gram-negative multidrug-resistant bacteria.

Methods: The study was planned as a retrospective cohort study. Patients aged 18 years and older who were hospitalized between January 01, 2015, and January 01, 2020, diagnosed with ventilator-associated pneumonia, and had Gram-negative multidrug resistant pathogen was detected in blood and/or bronchoalveolar lavage fluid specimen or quantitative endotracheal aspirate cultures were included in the study.

Results: A total of 370 patients were included in the study. Median age of the patients was 74 (19-95) years. Most frequent bacteria was Acinetobacter baumannii (52.4%). Resistance to ceftriaxone, meropenem, and colistin was 99%, 68%, and 4%, respectively. 7-day and 21-day mortality rates were 38.3% (n=142) and 85.1% (n=315). In multivariate analysis, 7-day mortality was associated with a Charlson comorbidity index score of ≥4, and risk factors for 7-day mortality were septic shock, amikacin resistance, and white blood cell count ≥15000/mm3. Advanced age was found to be a risk factor for 21-day mortality, and a high Acute Physiology and Chronic Health Evaluation II score and a high Charlson comorbidity index score were associated with 21-day mortality. It was found that the risk of 7-day mortality in patients with tracheostomy was lower than in patients without tracheostomy.

Conclusion: Consideration of clinical scoring systems, closer monitoring of elderly patients, following-up with tracheostomy, may provide a decrease in mortality of ventilator-associated pneumonia, caused by multidrug resistant pathogens.

Keywords: Mortality, multidrug resistance, pneumonia, risk factors, antibiotic resistance

DOI: 10.5798/dicletip.1220921

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Gram-Negatif Çoklu İlaç Dirençli Bakterilerin Etken Olduğu Ventilatör ile İlişkili Pnömonili Hastalarda 7-Günlük ve 21-Günlük Mortaliteyi Etkileyen Risk Faktörleri

Öz

Amaç: Gram negatif çoklu ilaç dirençli bakterilerin etken olduğu ventilatör ilişkili pnömoni insidansı artmaktadır ve erken ölüm oranı yüksektir.

Gram negatif çoklu ilaç dirençli bakterilerin neden olduğu ventilatör ilişkili pnömonide yaşlılığın, komorbiditelerin, Charlson komobidite indeks skorunun yüksekliğinin, Acute Physiology and Chronic Health Evaluation II skorunun yüksekliğinin, lökositozun, C-reaktif protein seviyesi yüksekliğinin, ampirik antibiyotik tedavisinin ve antibiyotik direncinin 7 günlük ve 21 günlük mortalite üzerine etkilerini araştırmayı amaçladık.

Yöntemler: Çalışma retrospektif kohort çalışması olarak planlandı. 01 Ocak 2015 - 01 Ocak 2020 tarihleri arasında hastaneye yatırılan, ventilatör ilişkili pnömoni tanısı konulan ve kan ve/veya bronkoalveolar lavaj sıvısı örneğinde veya kantitatif endotrakeal aspirat kültürlerinde çoklu ilaç dirençli gram negatif bakteri saptanan 18 yaş ve üzerindeki hastalar çalışmaya dahil edildi.

Bulgular: Çalışmaya toplam 370 hasta alındı. Hastaların ortanca yaşı 74 (19-95) idi. En sık görülen bakteri Acinetobacter baumannii (%52,4) idi. Seftriakson, meropenem ve kolistine direnç sırasıyla %99, %68 ve %4 idi. 7 günlük ve 21 günlük mortalite oranları %38,3 (n=142) ve %85,1 (n=315) idi. Çok değişkenli analizde, 7 günlük mortalite ile Charlson komorbidite indeks skoru ≥4 olması ilişkili bulundu, ayrıca 7 günlük mortalite için risk faktörlerinin septik şok, amikasin direnci ve beyaz küre sayısının ≥15000/mm3 olduğu belirlendi. İleri yaş 21- günlük mortalite için risk faktörü olarak bulundu ayrıca yüksek Acute Physiology and Chronic Health Evaluation II skoru ve yüksek Charlson komorbidite indeks skoru 21 günlük mortalite ile ilişkili bulundu. Trakeostomili hastalarda 7 günlük mortalite riskinin trakeostomisiz hastalara göre düşük olduğu saptandı.

Sonuç: Klinik skorlama sistemlerinin dikkate alınması, yaşlı hastaların daha yakından izlenmesi, trakeostomi ile takip edilmesi, çoklu ilaç dirençli patojenlerinin neden olduğu ventilatör ilişkili pnömoni mortalitesinde azalma sağlayabilir.

Anahtar kelimeler: Mortalite, çoklu ilaç direnci, pnömoni, risk faktörleri, antibiyotik direnci.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is one of the most frequently seen infectious diseases in intensive care unit[1–3]. In studies, VAP-related mortality is 14-70%[4,5]. It is contemplated that independent risk factors, increasing VAP-related mortality, are comorbidities, sepsis, acute respiratory distress syndrome (ARDS), old age, Acinetobacter baumannii infection, antibiotic resistance, and inappropriate antibiotic treatment[4,6,7]. These studies in literature have been traditionally conducted on the basis of 28-60-day mortality. However, the question of which factors are associated with early mortality in patients with VAP diagnosis, remains unanswered.

Multidrug resistance (MDR) bacteria was defined as acquired non-susceptibility to at least one drug in three or more antimicrobial categories[8]. Increase in gram-negative MDR infection poses a global threat[9–11]. In VAP, associated with gram-negative MDR pathogens, mortality rates were determined as 62.5% to 65.8%[3,12]. In Guidelines, in empirical treatment of VAP, two anti-pseudomonals plus one antimicrobial, which is effective against Methicillin-resistant Staphylococcus aureus are recommended to be used in combination[13]. A. baumannii is one of the most common gram-negative MDR bacteria in VAP[2,6,14,15]. Since A. baumanii is resistant to majority of the agents, recommended in guidelines, adequate efficacy can not be reached with empirical treatment[16]. Therefore, clinicians working in intensive care units with a high incidence of A. baumannii, find it difficult to choose effective and correct treatment for VAP patients.

In this study, determination of antibiotic resistance profile of bacteria in VAP caused by MDR pathogens, old age, chronic diseases, APACHE II score, Charlson comorbidity index score (CCIS), white blood cell count (WBC), C-reactive protein (CRP) level, empirical antibiotic treatment selection and antibiotic resistance. It

was aimed to determine the relationship between the profile of the patient and the 7-day and 21-day mortality.

METHOD

The hospital is a university hospital in Anatolia with 47 intensive care unit beds. A single-center, retrospective cohort study has been made. Patients of 18 years of age and over, who have been treated in intensive care unit between January 1, 2015 and January 1, 2020, followed-up with mechanical ventilation for more than 48 hours, diagnosed with VAP and with positive blood and/or broncho-alveolar lavage liquid and/or quantitative endotracheal aspirate (ETA) cultures, were included in study. ETA specimens were examined with microscopy. Culture results for ETA specimens with epithelial cell count greater than 10 or polymophnuclear leukocyte count less than 25, were excluded. When assessing culture results for ETA specimens, comprising two or more different bacteria in the same culture, microscopic examination results were considered. Bacteria, deemed as dominant bacteria as a result of microscopic examination, was included in study and the result, deemed as contamination was excluded. Repeating positive culture results (second result and subsequent results), were excluded from study. First and second endpoints were determined as 7-day and 21-day mortality, respectively. Study was approved by Niğde Ömer Halisdemir University ethics committee (Date: 04.10.2019, protocol number: 2019/27). Study was performed in compliance with ethical standards of Helsinki Declaration of 1975. Data were collected through the hospital's electronic system.

Age, sex, APACHE II score, CCIS, classification of sepsis or septic shock, mortality duration, WBC, CRP, use of antibiotic in the last one month, surgical operation in the last 90 day, antibiotic susceptibility profile and identification of microorganism, drugs (antibiotics, sedatives, total parenteral nutrition, steroids in the last 30 day, immunosuppressive drugs (except steroids) in the last 90 day) at the time of culture sampling, acute disease (trauma or myocardial infarction), chronic diseases (diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), malignancy, chronic renal disease, hypertension, neurological disease (Alzheimer, cerebrovascular diseases (SVO), Parkinson's disease), congestive heart failure) data of the patients were recorded in the patient form.

Ventilator-associated pneumonia was defined as pneumonia occurred more than 48 hours after patients have been intubated and received mechanical ventilation. In case of new pulmonary infiltrate and clinical evidence, showing that infiltrate was of infectious origin, including new onset fever, purulent sputum, leukocytosis and decrease in oxygenation, the patient was accepted as pneumonia. The day when positive culture sampling was taken from the patient was considered the first day. 7-day mortality was defined a mortality, occurred within the first seven days after obtaining culture specimen. Patients, discharged from hospital to go home before day seven, were deemed as survive on day seven. Sepsis and septic shock were defined according to Sepsis-1 criteria[17]. Turbidimetric method was used for measurement of CRP. Automated system was used for measurement of WBC.

Culture results from bronchoalveolar lavage fluid specimen (≥104 CFU/ml) or ETA (≥105 CFU/ml) were deemed as positive. MDR bacteria was defined as acquired non-susceptibility to at least one drug in three or more antimicrobial categories. In case the bacteria were resistant to antimicrobial agent in treatment, antibiotic treatment was deemed as inappropriate antibiotic treatment. Intermediate susceptibility was classified as resistant. In case of resistance to all antibiotics in combination therapy, antibiotic treatment was deemed as inappropriate antibiotic treatment.

Bacterial identification and susceptibility were done using VITEK 2 system (bioMérieux, France). Bacteria identification and antibiotic susceptibility results were interpreted according to European Antimicrobial Susceptibility Test (EUCAST) criteria[18].

Statistical Analysis

For the primary end-point, the data analysis compared seven-day survivors with non-survivors. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). The Chi-Square test or Fisher's exact test statistics were used for comparison of categorical variables. Normality assumption was assessed through the Kolmogorov-Smirnov test. For the comparison of continuous measurements between groups, distributions were checked, Student T test was used for variables showing parametric distribution, and Mann Whitney U test was used for variables that did not show parametric distribution. Independent risk factors affecting mortality were determined using logistic regression analysis. The statistical analysis was performed using SPSS 23.0 program. A P-value lower than 0.05 was considered statistically significant.

RESULTS

Files of 15,002 patients, treated in intensive care unit, were examined (Figure 1). A total of 370 patients were included in the study. Median age for patients was 74.0 and 39.5% was female. The basic characteristics, comorbid diseases and laboratory data of the patients are given in Table 1. In Figure 2, and Figure 3, age, CCIS, WBC and CRP distribution are given.

Table I: Baseline characteristics of patients

	7-day Non-Survivors (n=142)		**7-day Survivors (n=228)**		**p[1]**	**21-day Non-Survivors (n=315)**		**21-day Survivors (n=55)**		**p[2]**
	(n)	(%)	(n)	(%)		(n)	(%)	(n)	(%)	
Age*	76 (19-95)		73 (19-94)		0.039	76 (19-95)		65 (19-94)		<0.001
Age≥80	48	33.8	67	29.4	0.372	111	35.2	4	7.3	<0.001
Female	57	40.1	89	39	0.832	130	41.3	16	29.1	0.088
Comorbidities										
Surgery history	26	18.3	46	20.2	0.659	57	18.1	15	27.3	0.113
DM	46	32.4	59	25.9	0.176	92	29.2	13	23.6	0.398
COPD	65	45.8	107	46.9	0.828	148	47.0	24	43.6	0.646
Cancer	16	11.3	14	6.1	0.079	28	8.9	2	3.6	0.188
CRF	17	11.9	26	11.4	0.868	40	12.7	3	5.5	0.122
ND	45	31.7	78	34.2	0.617	107	34.0	16	29.1	0.479
CHF	16	11.3	25	11	0.928	34	10.8	7	12.7	0.673
Hypertension	41	28.9	49	21.5	0.108	78	24.8	12	21.8	0.639
TRCH	9	6.3	40	17.5	0.002	42	13.3	7	12.7	0.903
Septic shock	84	59.2	62	27.2	<0.001	132	41.9	14	25.5	0.025
Bacteremia	26	18.3	48	21.1	0.521	59	18.7	15	27.3	0.144
Drugs, laboratory parameters and clinical scores										
Sedatives	31	21.8	30	13.2	0.029	53	16.8	8	14.5	0.674
Steroids	18	12.7	30	13.2	0.893	42	13.3	6	10.9	0.622
TPN	66	46.5	86	37.7	0.096	126	40.0	28	47.3	0.312
Antibiotic used	81	57	133	58.3	0.807	181	57.5	33	60.0	0.725
Days between MV-pneumonia	9(2-79)		13(2-162)		0.007	11 (2-162)		11 (2-76)		0.901
CCIS*	2 (0-10)		2 (0-10)		0.012	2 (0-10)		1 (0-5)		0.001
CCIS ≥4	38	26.7	143	62.7	0.020	104	33.0	8	14.5	0.006
APACHE II **	23.72(±6.151)		22.37(±6.811)		0.090	23.37 (±6.177)		20.00 (±8.038)		0.001
APACHE II≥25	46	44.2	73	35.6	0.141	106	40.9	13	26.0	0.047
WBC /mm3*	13 (1-58)		11 (2-79)		0.003	12 (1-79)		11 (4-33)		0.186
WBC≥15000	79	55.6	83	36.4	<0.001	142	45.1	20	36.4	0.229
CRP (mg/L)*	172.5(16-578)		147.5(13-476)		0.001	161 (13-578)		147 (23-364)		0.169
CRP≥200 mg/L	60	42.3	61	26.8	0.002	105	33.3	16	29.1	0.536

p1 Comparison of those who survived seven-day and those who did not survive seven-day,
p2 Comparison of those who survived 21 days and those who did not survive 21 days,
*DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, ND: Neurological disorders, CHF: Congestive heart failure, TRCH: Tracheostomy, TPN: Total parenteral nutritionü, MV: Mechanical ventilation, CCIS: Charlson comorbidity index score, WBC: White blood cell count, CRP: C-reactive protein, * Median (Minimum-Maximum), ** Mean value and standard deviation.*

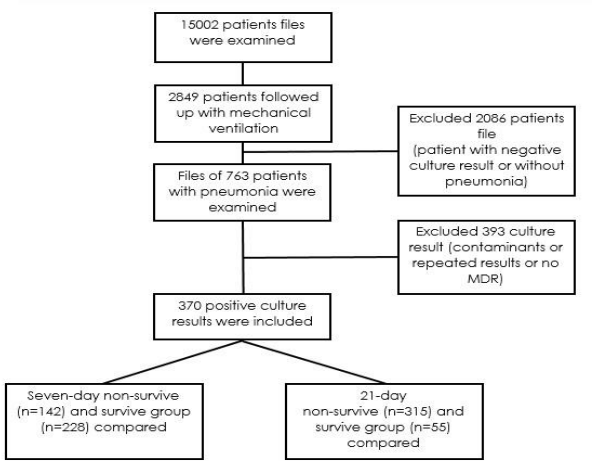

Figure 1: Flowchart of the study

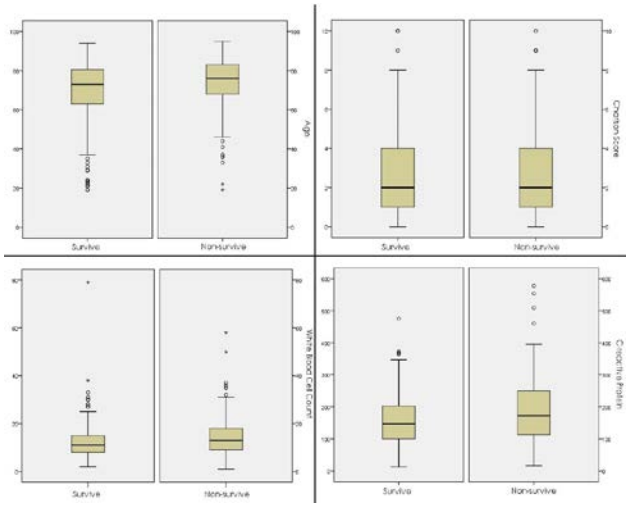

Figure 2: Distribution of age, Charlson comorbidity index score, white blood cell count and C-reactive protein level in 7-day mortality group

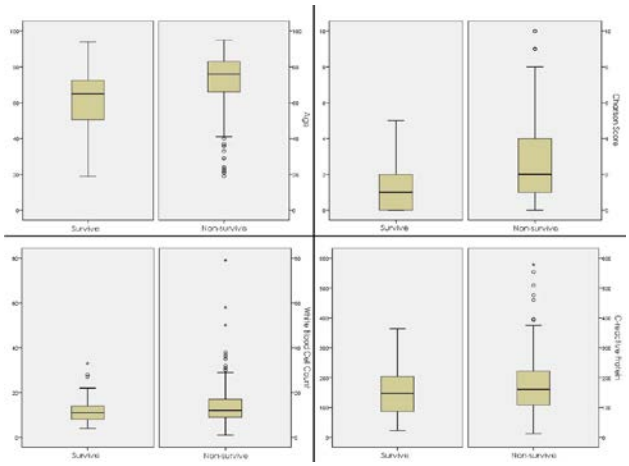

Figure 3: Distribution of age, Charlson comorbidity index score, white blood cell count and C-reactive protein level in 21-day mortality group

Most frequently seen bacteria was A.baumannii (52.4%). Distribution of microorganisms, empirical antibiotic treatment and antibiotic resistance pattern are given in Table 2. 7-day and 21-day mortality rates were 38.3% (n=142) and 85.1% (n=315).

In a univariate analysis, septic shock (OR:3.878 (2.488-6.044)) (p<0.001), WBC≥15000/mm3 (OR:2.191 (1.429-3.358)) (p<0.001), CRP≥200 mg/L (OR:2.003 (1.285-3.122)) (p=0.002), sedative treatment (OR:1.843 (1.060-3.205)) (p=0.029), CCIS≥4 (OR:1.706 (1.086-2.678)) (p=0.020), high CCIS (p=0.012), ciprofloxacin resistance (OR:1.703 (1.018-2.851)) (p=0.046), amikacin resistance (OR:1.695 (1.096-2.622)) (p=0.022), advanced age (p=0.039) and long time period between intubation and pneumonia diagnosis (p=0.007), were found as risk factors for 7-day mortality. Age≥80 (OR:6.938 (2.443-19.699)) (p<0.001), advanced age (p<0.001), CCIS≥4 (OR:2.896 (1.320-6.352)) (p=0.006), high CCIS (p=0.001), septic shock (OR:2.112 (1.106-4.033)) (p=0.025) and high APACHE II score (p=0.001), were found as risk factors for 21-day mortality. It was determined that follow-up with tracheostomy decreased 7-day mortality risk (OR:0.318 (0.149-0.678)) (p=002).

In multivariate analysis, it was determined that risk factors for 7-day mortality were septic shock (OR:3.662 (2.287-5.863)) (p<0.001), CCIS≥4 (OR:1.877 (1.144-3.081)) (p=0.013), amikacin resistance (OR:1.869 (1.159-3.014)) (p=0.01) and WBC≥15000/mm3 (OR:1.725 (1.077-2.763)) (p=0.023). Advanced age (OR:1.031 (1.009-1.053)) (p=0.005), high APACHE II score (OR:1.069 (1.016-1.125)) (p=0.01) and high CCIS (OR:1.220 (1.023-1.454)) (p=0.027) were found as risk factors for 21-day mortality. It was determined that follow-up with tracheostomy decreased 7-day mortality risk (OR:0.330 (0.148-0.735)) (p=0.007).

Table II: Distribution of microorganisms, antibiotics resistance, and antibiotherapy

	7-day Non-Survivors (n=142)		7-day Survivors (n=228)		p[1]	21-day Non-Survivors (n=315)		21-day Survivors (n=55)		p[2]
	n	%	n	%		n	%	n	%	
A. baumannii	78	54.9	116	50.9	0.448	163	51.7	31	56.4	0.527
E. coli	11	7.7	10	4.4	0.174	18	5.7	3	5.5	1.000
Klebsiella spp.	24	16.9	42	18.4	0.710	59	18.7	7	12.7	0.283
P. aeruginosa	23	16.2	55	24.1	0.069	67	21.3	11	20.0	0.831
Others	6	4.2	5	2.2	0.347	8	2.6	3	5.4	0.215
Antibiotic resistance										
Ceftriaxone	142	100	225	98.7	0.170	313	99.4	54	98.2	0.384
Cefepime	116	81.7	169	74.1	0.092	244	77.5	41	74.5	0.635
PIP-TAZO	110	77.5	169	74.1	0.468	238	75.6	41	74.5	0.872
IMP/C	98	69.0	149	65.4	0.467	211	67.0	36	65.5	0.824
Meropenem	100	70.4	155	68.0	0.622	218	69.2	37	67.3	0.775
Tigecycline	69	48.6	112	49.1	0.921	154	48.9	27	49.1	0.978
Colistin	8	5.6	8	3.5	0.328	14	4.4	2	3.6	1.000
Ciprofloxacin	116	81.7	165	72.4	0.041	240	76.2	41	74.5	0.792
TMP-SMX	123	86.6	207	90.8	0.209	283	89.8	47	85.5	0.334
Amikacin	95	66.9	124	54.4	0.017	190	60.3	29	52.7	0.291
Empirical antibiotic theraphy										
Ceftriaxone	21	14.8	24	10.5	0.073	35	11.1	10	18.1	0.375
PIP-TAZO	42	29.6	73	32.0	0.622	89	34.4	11	22.0	0.108
Carbapenem	54	38.0	93	40.8	0.598	124	39.4	23	41.8	0.732
Amikacin	5	3.5	7	3.1	0.812	12	3.8	0	0	0.141
Tigecycline	6	4.2	11	4.8	0.789	16	5.1	1	1.8	0.286
Colistin	15	10.6	20	8.8	0.567	28	8.9	7	12.7	0.369
Quinolones	11	7.7	18	7.9	0.959	26	8.3	3	5.5	0.596
Combined AB	38	26.8	58	25.4	0.778	85	27	11	20	0.276
Appropriate AB	37	26.1	57	25.0	0.820	81	25.7	13	23.6	0.744

p1 Comparison of those who survived seven-day and those who did not survive seven-day,

p2Comparison of those who survived 21 days and those who did not survive 21 days,

PIP-TAZO: Piperacillin-tazobactam, IMP/C: Imipenem-cilastatin, TMP-SMX: Trimethoprim-sulfamethoxazole, AB: Antibiotic

DISCUSSION

Average age of patients with VAP is high and have many chronic conditions[2,3,6]. Ciginskiene et al, determined that underlying chronic conditions increased mortality risk[3]. However, Zhou et al, concluded that comorbidities were not associated with 30-day mortality[4]. In our

study, no correlation between comorbid conditions and7-day or 21-day mortality was found. Different result in the study of Ciginskiene et al., may be caused by the definition of mortality as mortality, which occurs in hospital and failure to consider time to mortality[3]. In elderly, susceptibility to pneumonia is high due to frequent aspiration, impaired gagging reflex, decreased mucociliary activity and weak immune response, associated with central nervous system diseases[19]. Arayasukawat et al, determined that an age over 60 years, increased mortality risk by 2.1-fold[6]. We also determined that advanced age increased mortality risk. We contemplate that this could be caused by the difficulty for immune system to take pneumonia under control at advanced age, and slower tissue healing compared to young individuals. In our study, 7-day and 21-day mortality rates were 38% and 85%, respectively. In literature studies, 30-day mortality rates are between 14% to 70%[3,4,12]. Higher median age in the study compared to other studies, high rate of patients with A.baumannii infection, compared to other studies, may be the reasons for higher mortality rate in our study compared to other studies.

Leukocyte count is used in VAP diagnosis, sepsis diagnosis and in APACHE II scoring systems[13]. Although there are many studies, demonstrating the utility of CCIS and APACHE II scores in prediction of mortality in VAP, the role of severe leukocytosis in prediction of mortality is questionable[4,20]. Gardner et al., determined that in patients, diagnosed with pneumococcal pneumonia WBC count of 25000/mm3 and higher increased mortality risk by three times[21]. Povoa et al., determined that WBC was irrelevant with mortality in VAP[22]. We determined that WBC over 15000/mm3 increased mortality by 1.7 times. Povoa et al., did not determine any cut-off value for WBC and their comparison of mean WBC counts of patients and inclusion of only MDR factors in our study, may have caused the difference between results[22]. This result is significant because in literature, there are no studies, showing the correlation of leukocytosis with mortality in patients with VAP, caused by MDR bacteria. Zhou et al., determined that high APACHE II score was associated with 30-day mortality[4]. We found that the APACHE II score was associated with 21-day mortality, but not with 7-day mortality. We discovered that unlike APACHE II, CCIS score could be useful in prediction of both 7-day and 21-day mortality. We determined that high CCIS increased mortality risk by 1.2 times and in addition, CCIS of 4 or greater increased 7-day mortality risk by 1.8 times. Similar to our results, Rivera-Espinar, et al., have found that high CCIS increased mortality risk by 1.1 times[23]. These results show that in VAP patients, scoring systems had to be examined carefully in the prediction of mortality.

Tracheostomy is a common procedure performed in patients requiring prolonged mechanical ventilation. Siddiqui et al., have determined that tracheostomy had decreased VAP mortality[24]. However, Ju et al., found no correlation between tracheostomy and 30-day mortality in VAP, associated with A. baumannii[25]. We determined that 7-day mortality was lower in patients with tracheostomy compared to non-tracheostomy patients. Low VAP-associated 7-day mortality in patients with tracheostomy, is a new knowledge in literature. As a personal opinion, this result could be related to better oral hygiene and more effective aspiration due to tracheostomy, thereby a decrease in the number of bacteria, which reach the lungs of the tracheostomy patient.

It is suggested to consider local epidemiological data in empirical treatment of VAP[13]. However the question of which antibiotic decreases mortality rate in empirical treatment, has not

been fully answered. Cisneros, et al., concluded that in empirical treatment, use of meropenem or colistin did not affect mortality[26]. Salehi, et al., determined that there were no significant differences in terms of mortality between different antibiotic treatments[12]. Rivera-Espinar, et al., determined that appropriate empirical treatment did not affect mortality[23]. We found that there was no statistically significant difference in mortality between different antibiotic treatments. Rivera-Espinar, et al., found that carbapenem resistance did not increase mortality risk[23]. Cisneros, et al., determined that there was no significant correlation between meropenem and colistin resistance and mortality 26. We concluded that colistin, meropenem and imipenem resistances were not related to mortality. Despite numerous studies on meropenem and colistin resistances in the literature, studies on amikacin resistance are inadequate. This issue has not been studied in detail. We found that, infection with amikacin-resistant microorganism, increases 7-day mortality risk by 1.8 times. Amikacin is generally used in combination with beta-lactam antibiotics and they show a synergistic activity. In amikacin resistance, absence of such synergistic activity, might have mitigated the success rate of treatment. This is a new data for literature. It is valuable for understanding the importance of amikacin resistance with respect to mortality in MDR-associated VAP. In our resultswe, the reason for failure to find a correlation between commencement of empirical amikacin treatment with mortality risk, could be the initiation of empirical amikacin treatment in only 12 patients. Conduction of studies with greater number of patients, may explain the effect of empirical amikacin treatment on mortality risk. We think that this study will contribute to the literature in terms of determining local antibiotic resistance, evaluating the effects of amikacin resistance, CCIS, APACHE II, WBC, septic shock, advanced age and tracheostomy on mortality in VAP caused by gram-negative MDR bacteria. Limitations of the study: the study is a retrospective study, has been conducted in a single center and does not encompass world in general, some novel antibiotics, such as cephtasidim-avibactam could not be included in study since they were unavailable in hospital pharmacy during the term of study.

CONCLUSION

Based on the results, we think that considering the CCIS and APACHE II scoring systems and leukocytosis, monitoring the patients at high risk of developing VAP with tracheostomy, and being more careful in choosing the treatment of patients infected with amikacin-resistant microorganisms may be beneficial in reducing mortality in VAP patients.

Ethics Committee Approval: Study was approved by Niğde Ömer Halisdemir University ethics committee (Date: 04.10.2019, protocol number: 2019/27)

Conflict of Interest: The authors declared no conflicts of interest.

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

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