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The relationship between renal functions and multi-drug resistant organisms in patients with ventilator-associated pneumonia

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ABSTRACT

Objective: Despite the increase in the frequency of multi-drug resistant organism (MDRO) colonisation and infection in dialysis patients, it is not well known whether the risk of multi-drug resistant (MDR) pneumonia increases in mild-to-severe chronic kidney disease patients not undergoing dialysis. Therefore, we aimed to evaluate the relationship between renal functions and the risk of MDR ventilator-associated pneumonia (VAP) and the specific microbial pattern.

Patients and Methods: A total of 133 patients who developed VAP were divided according to their renal function into two groups, an estimated glomerular filtration rate of (eGFR) ≥ 60 mL/ min/1.73 m2 (high eGFR, n=65) and eGFR < 60 mL/min/1.73 m2 (low eGFR, n=68).

Results: The low eGFR group presented a significantly high MDRO ratio (p<0.01). With the decrease in eGFR, the frequency of gram-positive MDRO did not change (p=0.63), while the increase in gram-negative MDRO was statistically significant (p<0.01). Low eGFR was found to be an independent predictor for antimicrobial resistance. (Odds ratio, (OR): 2.821).

Conclusion: Among VAP patients, chronic renal failure is associated with increased MDRO infection. The eGFR may be used to identify mechanically ventilated patients with a high risk of MDR pneumonia.

Keywords: Chronic kidney disease, Glomerular filtration rate, Multiple drug resistance, Risk factors, Ventilator-associated pneumonia

1. INTRODUCTION

Patients receiving invasive mechanical ventilation (MV) suffer most commonly from ventilator-associated pneumonia (VAP) as a nosocomial infection. Approximately half of the antibiotic expenditure in the intensive care unit (ICU) is due to VAP treatment [1]. Antibiotic resistance poses an increasing threat due to the rise of infections caused by multi-drug resistant organisms (MDRO)s [2]. Even mild and moderate reductions in the estimated glomerular filtration rate (eGFR) (e.g., 30-59 mL/min/1.73 m^2) are a significant risk factor for infection [3]. Patients suffering from chronic renal failure (CRF) experience a more frequent use of antibiotics [4] and hospitalisations due to the high infection rates [5], which leads to an increase in exposure to MDROs [6]. In addition, in patients with CRF, the risk of hospitalisation and mortality due to pneumonia is increased [7]. Although, MDRO infection is more frequently detected in dialysis patients [8], it is not known enough whether the risk of multi-drug resistant (MDR) pneumonia increases in mild-to-severe chronic kidney disease (CKD) (eGFR < 60 mL/ min/1.73 m^2) patients not receiving dialysis. In this study, we aimed to assess the relationship between renal functions and MDR VAP risk and the specific microbial pattern in pneumonia patients.

2. PATIENTS and METHODS

Study population

This prospective observational study was conducted on adult patients intubated and receiving MV for at least 48 hours in the 42-bed surgical and medical ICU in Konya Numune Hospital. The study was performed with the approval of the Ethics Committee of Necmettin Erbakan University Medical School (no. 2019/1901) between August 2019 and January 2021. Also, the study has been included in the index of the National Clinical

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Trial website (www.clinicaltrials.gov: NCT04833231). Informed consents were obtained from the patients participating in the study or their relatives.

Inclusion and exclusion criteria

Patients whose age was 18 years or above, clinically suspected of VAP as defined in the American Thoracic Society (ATS) guidelines [9], with a Clinical Pulmonary Infection Score (CPIS) > 6 [10], and with no clinical evidence of any infection when admitted to the ICU, were included in the study.

Patients suffering from acute kidney injury, renal replacement treatment (RRT), dialysis, renal transplantation, active tuberculosis, malnutrition, immunosuppression (neutropenia, HIV positivity, transplantation, prednisone treatment of ≥ 20 mg/day, etc.), presenting any extrapulmonary infection other than VAP at the time of inclusion in the study, as well as respiratory cultures with fungal agents, normal flora or no growth, were not included in the study.

Definitions

Pneumonia developing at least 48 hours after the onset of endotracheal intubation and MV was defined as VAP. The formula determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was used to calculate the eGFR values based on the measured serum creatinine concentrations [11]. The renal functions of the patients were recorded at the time of admission to the ICU and the diagnosis of VAP. The eGFR values on the day of diagnosis were used to divide the patients with pneumonia into two groups, ≥ 60 mL/ min/1.73 m^2 and < 60 mL/ min/1.73 m^2. An eGFR below 60 mL/ min/1.73 m^2 (low eGFR) was defined as renal dysfunction [3]. Comorbidities and the severity of underlying diseases were assessed according to the Charlson comorbidity index [12]. In contrast, the Acute Physiology and Chronic Health Evaluation score (APACHE II) was used in patients at the beginning of the infection to assess the illness severity [13].

Pan-drug resistant (PDR), extensive-drug resistant (XDR) and MDR pathogens were identified based on the study of Magiorakos et al [14]. XDR and PDR organisms were evaluated as MDR. Detecting more than one potentially pathogenic microorganism was defined as polymicrobial pneumonia [15]. In patients with polymicrobial VAP, finding at least 1 MDR organism was classified as MDR. Death from any cause occurring within 28 days since the VAP onset was defined as 28-day ICU mortality.

Study protocol

One hundred and thirty-three VAP patients without nosocomial infection were prospectively and consecutively included in the study. The diagnosis of VAP was achieved based on clinical and microbiological criteria. Confirmation of VAP diagnosis in patients clinically suspected of VAP and CPIS > 6 was accomplished by observing > 10^4 colony forming units (cfu)/ml in the conventional culture of tracheobronchial aspirate [16].

Also, blood and urine cultures were obtained to discard other possible nosocomial infections. VITEK 2 healthcare system (bioMérieux SA, Marcy-l'Étoile, France) was utilised for antimicrobial susceptibility tests. The guidelines provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST 2019) were used in the interpretation of the results of the Minimal inhibitory concentration (MIC) test [17]. Organisms with intermediate susceptibility were considered antimicrobial-resistant.

Sample size

In order to define the minimum sample size, a power analysis by a Fisher's exact test was performed using the publicly available statistical software G*Power, version 3.1. Prior to the beginning of the study, no published information about the effect of renal functions on MDR pneumonia in critically ill patients was available; as such, a sample size estimation based on previous studies was not possible. Therefore, we first conducted a pilot study on 30 patients with the same methods used in the main study. In our preliminary study, MDROs were observed in 60% of the individuals in the high eGFR group and 87% of the low eGFR group. In order to detect a significantly different rate of MDROs among the two groups, a power analysis was carried out using a 2-sided confidence level of 95% ($p<0.05$) and a power of 90%. Considering the 10% dropout rate, the sample size was finally calculated as at least 132 patients.

Statistical Analysis

SPSS statistics package version 21.0 was used to analyse the data. Number and percentage (%) were used in the definition of categorical variables, while mean ± standard deviation was applied for continuous variables. A comparison of the categorical variables was made according to their suitability with Pearson's chi-square or Fisher's exact tests. The Independent Samples t-test was used to analyse continuous variables presenting a normal distribution, while the nonparametric Mann-Whitney U test was used for those that did not. The evaluation of risk factors in the acquisition by different eGFR groups of MDR bacteria independently associated with the tracheobronchial culture result was made by multivariate logistic regression. The appropriateness of the models was assessed by the Hosmer Lemeshow goodness of fit test [18]. The significance of the association was expressed with the 95% confidence interval as the odds ratio. The Receiver Operating Characteristic (ROC) analysis was run to measure the predictive capacity of eGFR levels in the differentiation of antimicrobial resistance status. The area under the curve (AUC) and a 95% confidence interval (CI) were recorded. Youden's indices were used to determine the best discriminatory cut-off values [19]. In all tests $p<0.05$ values were regarded as significant.

3. RESULTS

In the observed period, of 248 patients clinically suspected of VAP, 133 were confirmed microbiologically and included in the study. Table I shows the demographic data. Hypertension was the most common underlying systemic disease, occurring in 38% of the patients. In the eGFR < 60 mL/min/1.73 m^2 group,

the frequency of diabetes and hypertension and the length of the stay in the ICU were significantly higher than in the eGFR ≥ 60 mL/min/1.73 m^2 group. A significant difference in terms of other data was not detected among the groups (Table I).

Table I. *Baseline characteristics of patients with ventilator-associated pneumonia.*

Variables	eGFR, mL/min/1.73 m^2		p value
	≥ 60 (n = 65)	< 60 (n = 68)	
Age in years	62 ± 11.9	65 ± 12.6	0.48
Gender, male, n (%)	34 (52)	34 (50)	0.71
Charlson index	2.3 ± 0.31	2.4 ± 0.37	0.36
Co-morbidities, n (%)			
Hypertension	18 (28)	32 (47)	< 0.01*
Diabetes mellitus	10 (15)	17 (25)	0.04*
Malignancy	5 (8)	6 (9)	0.7
Cardiovascular diseases	15 (23)	21 (31)	0.15
Serebrovascular diseases	11 (17)	16 (24)	0.14
Hepatic disease	3 (5)	4 (6)	0.6
COPD	13 (20)	14 (21)	0.84
Rheumatical diseases	3 (5)	5 (7)	0.38
Peptic ulcus	4 (6)	6 (9)	0.35
Main causes of ICU admission, n (%)			
Medical	50 (77)	49 (72)	0.35
Surgery/Trauma	15 (23)	19 (28)	
APACHE II	21.6 ± 7.7	23.5 ± 7.2	0.15
CPIS	7.3 ± 0.4	7.4 ± 0.3	0.22
Positive blood culture, n (%)	4 (6)	6 (9)	0.35
Vazopressor use, n (%)	12 (18)	15(22)	0.47
Previous antibiotic use within 14 days			
prior to VAP onset, n (%)	46 (71)	54 (79)	0.15
ICU length of stay(days)	16 ± 6.8	20 ± 7.2	0.04*
28-day ICU mortality, n (%)	25 (38)	30 (44)	0.37

*Data shown as mean ± standard deviation or n (%). * eGFR ≥ 60 vs eGFR < 60 group, (p<0.05). eGFR: estimated glomerular filtration rate, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, APACHE II: Acute Physiological and Chronic Health Evaluation, CPIS: Clinical Pulmonary Infection Score, VAP: ventilator-associated pneumonia.*

Based on previous discoveries, the probable factors for acquiring MDR bacteria were tested using logistic regression. According to univariate logistic regression, the predictors with p<0.2, including age, gender, Charlson comorbidity index [12], hypertension, diabetes mellitus, cardiovascular disease, APACHE II and previous use of antibiotics, were included in the multivariate analyses [13]. As described in Figure 1, in the multivariate logistic regression model, low eGFR was found to be an independent predictor for antimicrobial resistance. The odds of infections by MDROs were independently associated with low eGFR (Odds ratio, OR: 2.821, 95% CI: 1.290-6.165) and negatively associated with high eGFR (OR: 0.355, 95% CI: 0.162-0.775, p = 0.009). In addition, the interaction between age and MDRO risk by low eGFR was also positively associated (OR: 1.122, 95% CI: 1.026-1.429, p=0.012). Male patients presented a lower risk of MDROs, while patients with diabetes mellitus and previous use of antibiotics had a higher risk of MDROs in both high and low eGFR categories. Although, the OR of MDROs were higher across comorbidities in patients with low eGFR, they were not statistically significant except for diabetes mellitus.

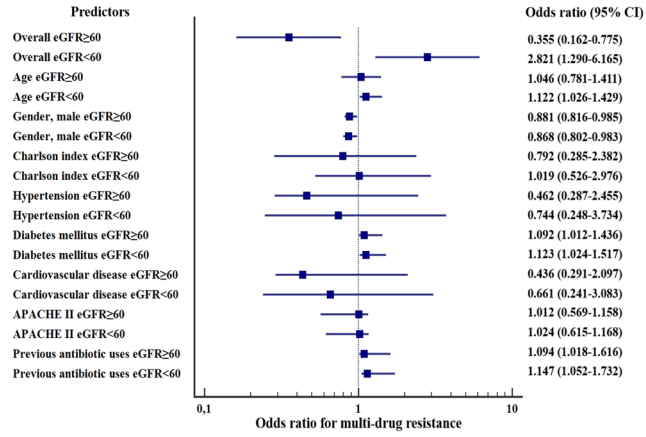

Figure 1. *Risk factors for antimicrobial resistance in patients with ventilator-associated pneumonia. eGFR: estimated glomerular filtration rate; APACHE II: Acute Physiology and Chronic Health Evaluation II; CI: confidence interval*

When pathogenic microorganisms were evaluated, 94 (71%) MDRO isolated from tracheobronchial aspirate culture showed a different microbiological pattern varying according to eGFR groups. Compared to the eGFR ≥ 60 group, there was a significant increase in the MDRO rate in the eGFR < 60 group (p<0.01). While with the decrease in eGFR, the frequency of gram-positive (Gr +) MDRO did not change (p=0.63), the increase in gram-negative (Gr –) MDRO was statistically significant (p<0.01). Predominantly, MDROs as *Enterobacteriaceae spp.* and non-fermenting Gr (-) bacilli were found.

The frequency of polymicrobial MDR pneumonia was similar in both groups. When the cases of monomicrobial pneumonia were evaluated, although there was an overall increase in the incidence of MDR monomicrobial pathogens with a decrease in eGFR, this increase was not statistically significant except for *Enterococcus spp.* (p=0.04) (Table II, Figure 2).

Since it was shown that eGFR has a significant relationship with MDR pathogens in VAP patients, ROC analysis was used to evaluate the predictive capacity of eGFR levels in the differentiation of antimicrobial resistance status. The area under curve (AUC) value of the ROC curve had a fair diagnostic value of 0.795 (95% CI, 0.704-0.886; p < 0.001). With the Youden criterion, the 61.5 mL/ min/1.73 m^2 cut-off value of eGFR was found to have 75% sensitivity, 74% specificity, 88% positive predictive value (PPV), 55% negative predictive value of (NPV) and 74% of overall accuracy in the diagnosis of MDR infection (Table III, Figure 3).

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Table II. *Pathogens associated with ventilator-associated pneumonia*

Pathogen	eGFR, mL/min/1.73 m²		p value
	≥ 60 (n = 65)	< 60 (n = 68)	
MDRO, n (%)	39 (65)	55 (81)	< 0.01*
Polimicrobial	7 (11)	8 (12)	0.75
Monomicrobial			
NFGNB	12 (18)	17 (25)	0.18
Pseudomonas aeruginosa	7 (11)	9 (13)	0.33
Acinetobacter baumannii	5 (8)	8 (12)	0.2
Enterobacteriaceae spp	9 (14)	13 (19)	0.22
Staphylococcus aureus	4 (6)	7 (10)	0.21
Enterococcus spp.	3 (5)	7 (10)	0.04*
Others	4 (6)	3 (4)	0.48
Gram (+)	16 (25)	15 (22)	0.63
Gram (-)	23 (35)	40 (59)	< 0.01*

*Data shown as mean ± standard deviation or n (%). * eGFR ≥ 60 vs eGFR < 60 group, (p<0.05). eGFR: estimated glomerular filtration rate, MDRO: multi-drug resistance organism, Gram (+): gram-positive bacteria, Gram (-): gram-negative bacteria, NFGNB: nonfermenting gram-negative bacilli*

Table III. *Predictive value of different cut-offs of eGFR in differential diagnosis between MDR and Non-MDR ventilator-associated pneumonia*

eGFR cut-off value (mL/min/1.73m²)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
50	56	82	88.5	44.4	3.14	0.53
54.5	63	77	86.7	46.1	2.72	0.48
61.5	**75**	**74**	**87.5**	**54.7**	**2.9**	**0.34**
68	81	67	85.3	59.1	2.43	0.29
72	83	62	83.8	60	2.16	0.28

Data are presented as %, unless otherwise stated. MDR: multi-drug resistant, eGFR: estimated glomerular filtration rate, PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio.

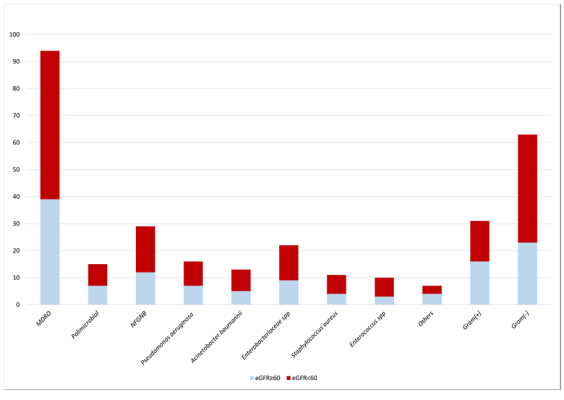

Figure 2. *Frequency distribution of specific bacterial in the culture of tracheobronchial aspirate by eGFR categories. MDRO: multi-drug resistant organism; NFGNB: nonfermenting gram-negative bacilli*

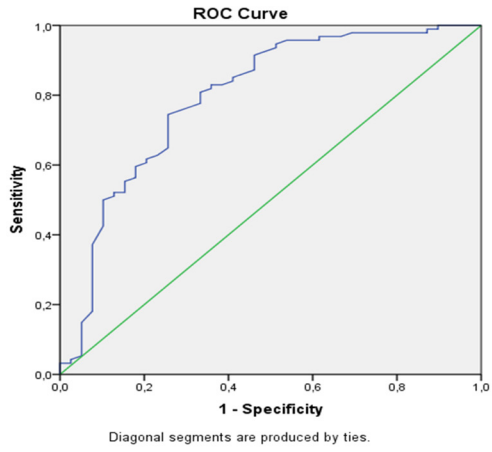

Figure 3. *Receiver Operating Characteristic (ROC) curve for eGFR (AUC: 0.795, 95% CI, 0.704-0.886) for discrimination between MDR and Non-MDR pneumonia*

4. DISCUSSION

In the present study, the characteristics of VAP patients suffering from MDRO infections associated with different eGFR categories were identified. Based on the multivariate analysis, decreased eGFR, advanced age, diabetes mellitus and previous use of antibiotics were independently associated with an actual resistant infection, while the male gender was independently associated with protection against MDRO infection. In addition, the eGFR cut-off > 61.5 mL/min/1.73 m² could assist in excluding MDR VAP. Therefore, in patients clinically suspected of VAP and with microorganisms found in the direct microscopic examination of respiratory specimens, eGFR levels may help determine an appropriate empirical antimicrobial therapy that includes MDROs. Also, mechanically ventilated patients with impaired renal function should be carefully monitored as a high-risk group for MDR VAP.

There is an increased prevalence of MDROs in end-stage renal disease (ESRD)-patients or Stage 5 CKD [20] due to accompanying immune system deficiencies [8,21]. In addition, hemodialysis (HD) patients become more prone to nosocomial infections, especially those with ESRD-producing pathogens [22]. Shorr et al., showed that in patients with healthcare-associated pneumonia, long-term hemodialysis is an independently associated risk factor for antibiotic-resistant pathogen infections [23]. However, according to our knowledge, data on whether the risk of MDR infection increases in patients with kidney dysfunction and mechanically ventilated without ESRD is limited. Su et al., showed that, in hospitalised patients with infections, the risk of MDR infection is increased even in patients with mild and moderate renal failure [24]. Our results showed that decreased eGFR levels entail independent risk factors for MDR VAP.

In the present research, the diagnostic ability of eGFR to differentiate infections caused by MDR or non-MDROs was

evaluated. The best eGFR cut-off value was measured at the onset of suspected VAP, 61.5 mL/min/1.73 m^2, demonstrated a PPV of 88% and designated as positive 75% of the patients with MDR infection. Also, the eGFR had adequate predictive power for MDROs in VAP patients (AUC: 0.795). These results indicated that eGFR has clinical value for recognising MDR infection. Therefore, it can be useful to adjust the treatment by excluding false-negative diagnoses of MDR VAP. However, the risk of unnecessary antibiotic treatment must be considered.

Gram-Negative Bacilli (GNB) were the predominant pathogens in VAP. Nonfermenting GNB, *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Acinetobacter baumannii*, were commonly isolated and carried a potential for MDR VAP. However, the risk of colonisation by antimicrobial-resistant Gr (-) organisms increased due to the frequent exposure of CKD patients to healthcare settings and antibiotics. Vicas et al., showed that 28% of hemodialysis patients were colonised with Gr (-) pathogens. Furthermore, 20% of the patients had one of these MDR Gr (-) pathogens during the 6-month follow-up period [25]. Jamil et al., studied the MDR pattern of Gr (-) pathogens isolated from patients immunocompromised for CKD and renal transplant. It was demonstrated that there was a significant increase in antibiotic resistance in patients with chronic renal failure [26]. In the study conducted by Su et al., in non-hemodialysis CKD patients, the frequency of Gr (-) MDROs increased with the decrease in renal functions [24]. The significantly increased frequency of Gr (-) MDRO in kidney dysfunction patients observed in our study was consistent with previous results.

The risk factors for MDR pathogens in pneumonia patients are recognised by the guidelines of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) [9]. In addition, studies conducted with heterogeneous patient populations have demonstrated various risk factors, including age, diabetes mellitus, immunosuppression and severe underlying disease [27,28]. However, a few studies reported conflicting results on the association of age with the risk of MDR infections. Micek et al., in an international multicenter study, examined the risk factors for MDR strains in *P. aeruginosa* nosocomial pneumonia. A lower age was found to be independently associated with pneumonia by MDR *P. aeruginosa* [29]. However, in studies conducted with Gr (-) bacteremia and VAP patients, advanced age was identified as a risk factor for MDR organisms [30-32]. Similar to previous studies, in our study, advanced age, diabetes mellitus and the prior use of antibiotics were determined as independently associated MDR risk factors for VAP in patients with reduced renal functions.

The main characteristic of acute kidney injury (AKI, formerly acute renal failure) is the rapid decline in the excretory function of the kidney, often with oliguria, which usually develops between hours and days. The prevalence of this complication, which is 10%-15% in hospitalised patients [33], exceeds 50% in ICU patients [34]. Discerning among AKI and/or CKD _ must be made in patients with an abnormal kidney function of unspecified duration. AKI before admission may be indicated by reduced serum creatinine after hospitalisation [35]. In the present study, the medical history and baseline renal functions were recorded at the time of admission to the ICU, and then, the renal functions at the time of VAP diagnosis were compared with the previous results. In this way, the decrease in eGFR levels due to acute kidney dysfunction in patients suffering from pneumonia was limited as much as possible.

Studies have shown that values of 105 mL/min/1.73 m^2 eGFR and above may be associated with malnutrition and increase the risk of infection. Malnutrition leads to susceptibility to infection, particularly by affecting cell-mediated immune function, and, in return, the infection affects the nutritional status [36]. The loss of muscle mass in older patients contributes to high eGFR by causing low serum creatinine levels. Concurrently, in elderly patients, malnutrition, chronic inflammation and cachexia tend to occur [37]. James et al., showed an association between mortality risk and hospitalisation due to pneumonia and an eGFR ≥ 105 mL/ min/1.73 m^2. He suggested that the reduction of muscle mass associated with chronic diseases would reduce creatinine formation and, therefore, eGFR would be overestimated [38]. Xu et al., found that elderly patients in the highest eGFR category had an increased risk of community-acquired infections [3]. However, Su et al., detected no significant difference in the MDR infection risk in individuals with eGFR ≥ 105 mL/min/1.73 m^2 [24]. In our research, due to chronic diseases, malnutrition risk and the advanced average age in mechanically ventilated patients with severe disease, the real eGFR could be potentially incorrectly calculated. Therefore, the high eGFR category included levels of 105 mL/min/1.73 m^2 and above.

The current study has several strengths. First, the evaluation of renal functions in the admission to the ICU is an important indicator of the acuteness or chronicity of the eGFR decrease at the time of pneumonia diagnosis. Excluding AKI patients from the study provided a more objective evaluation of CKD. Second, the use of eGFR as a renal function indicator. Our results are compatible with routine practice, as clinical guidelines suggest using eGFR in the evaluation of renal functions. Our study also has several limitations. First, we used serum creatinine to evaluate renal function. Since, serum creatinine depends on muscle mass, calculated eGFR values may be higher in patients with severe disease [39]. Second, the deterioration in renal functions of patients in the ICU could be caused by different reasons, including other chronic diseases. These unmeasured factors and comorbidities may have affected the relationship between eGFR and MDR VAP. Third, despite the VAP confirmation by quantitative microbiology, false positive and negative results are possible, and therefore, this may affect the results associated with kidney failure.

Conclusion

In this study, an association of renal dysfunction with an increased MDR pneumonia risk was found. In patients suffering from renal dysfunction and clinically suspected of VAP, microbiological culture results should be closely monitored, and the potential of possible factors resistant to empirical antibiotherapy should be considered.

Compliance with the Ethical Standards

Ethical Approval: The study was performed with the approval of the Ethics Committee of Necmettin Erbakan University Medical School (no. 2019/1901) between August 2019 and January 2021. Informed consents were obtained from the patients participating in the study or their relatives.

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Conflict of Interest: The authors have no potential conflicts of interest to declare.

Authors' contributions

OI: Conceptualization, writing-original draft, formal analysis, investigation, supervision, data curation, AI: project administration, methodology, validation, visualization, software, writing-review and editing.

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