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Original Article

Risk factors for infections from multidrug-resistant organisms in patients with chronic obstructive pulmonary disease and pulmonary infections and the related nursing interventions

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Abstract: Objective: This study aimed to explore the risk factors for infections from multidrug-resistant organisms (MDRO) in patients with chronic obstructive pulmonary disease (COPD) and pulmonary infections and the related nursing interventions. Methods: A prospective analysis was performed on 278 patients with COPD and pulmonary infections admitted to the respiratory department or the intensive care unit, including 128 patients with MDRO infections and 150 patients without MDRO infections. Blood samples were collected from the patients to test the markers for bacterial culture and the serum concentrations of procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA). We assessed the diagnostic value of PCT, CRP, and SAA for MDRO, investigated the distributions of MDRO in different years, and explored the risk factors for MDRO infections. Results: The PCT, CRP, and SAA concentrations were higher in the patients from the MDRO infection group than they were in the patients from the non-MDRO infection group (all $P < 0.001$). The areas under the receiver operating characteristic curve for MDRO diagnoses were 0.792 using PCT, 0.811 using CRP, 0.755 using SAA, and 0.842 using a joint test of the three factors. The patients with MDRO infections were mainly infected with carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant Enterobacteriaceae. The distributions of the MDRO infection strains were statistically different among the different years ($P < 0.05$). A multivariate regression analysis identified invasive treatment procedures, long-term bed rest, and increased SAA concentrations as independent risk factors for MDRO infections in COPD patients with pulmonary infections (all $P < 0.01$). Conclusion: The joint CRP, PCT, and SAA test is moderately effective in the early diagnosis of MDRO infections in COPD patients with comorbid pulmonary infections. Infections from carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant Enterobacteriaceae are the main types of MDRO infections. MDRO strains are distributed variously in different years. There are many risk factors for MDRO infections in COPD patients with pulmonary infections, so corresponding interventions are needed to reduce the MDRO infection rate.

Keywords: Multi-drug resistant organisms, inflammatory factors, pulmonary infections, distribution characteristics, risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction and commonly manifests as cough, sputum, and wheezing clinically [1]. It has a domestic incidence of 8.6%, mainly attacks the elderly, and is more common in men than in women [2]. COPD ranks fourth among the causes of death worldwide [3]. Inflammatory damage is mainly responsible for COPD onset [4]. Inflammatory factors can promote the development of COPD and induce or exacerbate infections in patients, among which pulmonary infections are the most common complications [5]. Suffering from long-lasting illnesses and comorbid pulmonary infections, COPD patients have weakened immunity and general defenses and are at a higher risk of getting infected with multi-drug resistant organisms (MDRO) due to the invasive procedures during their treatment [6, 7]. What's worse, the clinical abuse of antibiotics pro-

motes the prevalence of MDRO infections in COPD patients with pulmonary infections and seriously impairs patients' prognoses and quality of life [8]. MDRO infections can stimulate disease progression and hence cause a significant increase in mortality [9]. Also, MDRO infections attenuate the drug efficacy of antibiotics, which raises the treatment difficulty and increases patients' economic burdens [10]. The gold standard for clinical MDRO diagnosis is bacterial culture, but the positive rate of only 15% delays the treatment of MDRO infections [11].

Through an analysis of the MDRO bacterial flora distribution and the related risk factors in COPD patients with pulmonary infections, MDRO infections can be better prevented and controlled. This study analyzed the MDRO infection risk in COPD patients with pulmonary infections in the 363 Hospital and tested the related infection markers, seeking to provide a clinical reference for the prevention and control of MDRO infections in COPD patients with pulmonary infections.

Materials and methods

General clinical data

This study was approved by the Ethics Committee of 363 Hospital. All the patients signed a written informed consent. We recruited 532 patients with COPD and pulmonary infections admitted to the 363 Hospital from January 2017 to December 2019 as the study cohort and excluded 254 patients according to the exclusion criteria. Ultimately, 278 patients were included in this prospective study, and they ranged in age from 23 to 74 years, with an average age of 64.8±7.6 years. The study cohort included 128 patients with MDRO infections and 150 patients without MDRO infections.

Inclusion and exclusion criteria

Inclusion criteria: 1. Patients who met the diagnostic criteria for COPD [12], 2. Patients who met the diagnostic criteria for pulmonary infections: a. Newly-appearing cough, sputum, or the aggravated symptoms of respiratory system diseases, along with purulent sputum, with or without chest pain; b. Fever; c. Lung consolidation signs and (or) moist crackles; d. A white blood cell (WBC) count over 10×10^9/L or under 4×10^9/L, with or without left shift, e. Flaky or patchy infiltrating shadows, or interstitial changes on the chest x-ray, with or without pleural effusion. When the patients met either item a, b, c, or e plus item e, and the probabilities of tuberculosis, lung tumors, non-infectious interstitial lung diseases, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic infiltration, and pulmonary vasculitis were excluded, then a clinical diagnosis of pulmonary infections could be achieved [13], 3. Patients aged 18-75 years, and 4. Patients with positive bacterial sputum or blood culture results. Exclusion criteria: 1. Patients with congenital immune deficiencies or the previous use of immunosuppressive agents, 2. Patients with malignant tumors, 3. Patients with multiple bacterial infections according to the bacterial culture results, and 4. Patients who had taken antibiotics within 48 hours of the blood sampling.

Methods

Bacterial culture: The patients' blood and sputum were collected in accordance with the National Guide to Clinical Laboratory Procedures after their infections occurred and the samples were sent for testing three times [14]. The MDRO diagnostic criteria referred to "Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance" [15]. The common types of MDRO include carbapenem-resistant Enterobacteriaceae (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbidenes-resistant *Klebsiella pneumoniae* (CRKP), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus faecium* (VREFm). The tests were carried out on a WalkAway40 automatic microbial identification instrument (Japan, Siemens).

Blood markers for infections: After the infections occurred and before any antibiotics were used, 10 mL of blood was collected from the cubital vein of each patient and stored in two sterile tubes containing ethylenediamine tetraacetic acid (5 mL of blood in each tube) at 4°C for 15 minutes, followed by centrifugation at 1106.8 × g to separate the serum and plasma.

Table 1. Comparison of the basic patient data

Group	MDRO infection group (n = 128)	Non-MDRO infection group (n = 150)	χ^2/t	P
Sex ratio (Male/Female)	76:52	89:61	0.000	0.994
Age	63.9±9.5	65.1±8.2	1.131	0.259
Body mass index	21.03±3.69	21.16±3.79	0.288	0.773
Undergoing invasive treatment procedures before infections (yes/no)	37	23	7.518	0.006
Long-term bed rest (yes/no)	52/76	35/115	9.604	0.002
Comorbid diseases				
Hypertension	52	61	0.000	0.994
Type2 diabetic patient	54	69	0.407	0.524
Coronary heart disease	41	52	0.215	0.643

Note: MDRO: multi-drug resistant organisms.

The samples were then stored at -80°C. The WHB count was determined using the Coulter LH750 automatic blood cell analyzer (Beckman Coulter, USA). The concentrations of procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA) were measured using enzyme-linked immunosorbent assays on an automatic immunoassay analyzer (Germany, Siemens).

Outcome measures

The PCT, CRP, and SAA concentrations after the infections were measured and receiver operating characteristic (ROC) curves were plotted to demonstrate the diagnostic values of the PCT/CRP/SAA single and joint tests for MDRO.

The distribution of MDRO across different years and at different infection sites was examined.

The MDRO infection risk factors in COPD patients with pulmonary infections were identified using a multivariate logistic regression analysis.

Statistical analysis

The data analysis was performed with SPSS 17.0. The continuous variables were represented as the mean ± standard deviation (x ± sd) or by the M (P25, P75) if they did not follow a normal distribution. The data following a normal distribution and homogeneity of variances were analyzed using the independent sample t-tests, denoted by t, and the data not following a normal distribution and homogeneity of variances were analyzed using rank sum tests, denoted by χ^2. The count data was analyzed using Pearson chi-square tests and denoted by the chi-square. The ROC curves were plotted on Medcalc and the areas under the ROC curve (AUC) were calculated. The differences between the ROC curves were analyzed using Z tests. The risk factors for the MDRO infections in the COPD patients with pulmonary infections were analyzed using logistic regression analyses. The variables showing differences in the univariate analyses were subjected to the Ward method for variable screening. The inclusion level was a *P* value below 0.05 and the exclusion level was a *P* value over 0.1. The risk of declined psychological resilience was expressed using the adjusted odds ratio (the OR value). A *P* value below 0.05 indicated a difference was statistically significant.

Results

Comparison of the basic patient data

The differences between the two groups of patients were not statistically significant in terms of their sex ratios, ages, body mass indexes, or comorbid diseases (all P > 0.05). The proportion of cases undergoing invasive treatment procedures and the cases requiring long-term bedrest before the infections occurred were markedly higher in the MDRO infection group than they were in the non-MDRO infection group (all P < 0.01). More details are shown in **Table 1**.

Comparison of the infection blood markers

The length of the hospitalizations, the fever durations, and the PCT, CRP, and SAA concentrations were higher in the MDRO infection group than they were in the non-MDRO infection group (all P < 0.001). The comparison of the WBC counts in the two groups showed no

Table 2. Comparison of the infection blood markers

Group	MDRO infection group (n = 128)	Non-MDRO infection group (n = 150)	t	P
Length of hospitalization (d)	15.9±6.5	10.5±7.9	6.175	< 0.001
Fever duration (d)	10.5±6.2	7.5±4.4	4.712	< 0.001
PCT (μg/L)	0.98±0.65	0.48±0.27	8.594	< 0.001
CRP (mg/L)	63.78±28.97	17.54±9.78	18.379	< 0.001
WBC (× 10^9/L)	9.79±4.06	9.64±4.84	0.227	0.782
SAA (mg/L)	114.76±62.17	60.72±35.16	9.081	< 0.001

Note: PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; WBC: white blood cell; MDRO: multi-drug resistant organisms.

Table 3. Predicted and compared AUC of the MDRO infections using PCT, CRP, and SAA

Index	PCT (μg/L)	CRP (mg/L)	SAA (mg/L)	Joint test of the three factors
Cut-off value	0.765	32.145	119.623	
AUC	0.792	0.811	0.755#	0.842**,#,&&&
Sensitivity	0.649	0.818	0.466	0.822
Specificity	0.957	0.756	0.970	0.869
Standard error	0.023	0.029	0.027	0.019
95% CI	0.773-0.812	0.793-0.830	0.702-0.803	0.832-0.863

Note: Compared with the AUC of PTC, **P < 0.01; compared with the AUC of CRP, #P < 0.05; compared with the AUC of SAA, &&&P < 0.001. AUC: area under the curve; MDRO: multi-drug resistant organisms; PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A.

significant differences (P > 0.05). More details are shown in **Table 2**.

Diagnostic value of infection-related markers for MDRO infections

The AUC was 0.792 for the MDRO diagnoses using PCT, with a Youden index of 0.606, a specificity of 0.957, and a sensitivity of 0.649 when the cut-off value of the PCT concentration was 0.765 μg/L. The AUC was 0.811 for the MDRO diagnoses using CRP, with a Youden index of 0.574, a specificity of 0.756, and a sensitivity of 0.818 when the cut-off value of the CRP concentration was 32.145 mg/L. The AUC was 0.755 for the MDRO diagnoses using SAA, with a Youden index of 0.436, a specificity of 0.970, and a sensitivity of 0.466 when the cut-off value of the SAA concentration was 119.623 mg/L. The joint test of the three markers for the MDRO diagnoses was subjected to a logistic regression analysis to yield the equation of the best diagnostic model: Logit (P) = -5.098 + 7.923 × PCT + 7.453 × CRP + 7.346 × SAA. The risk probability of MDRO infections was determined, which referred to the probability of disease occurrence based on the risk factors ($P = +e^{-(-5.098+7.923\times PCT+7.453\times CRP+7.346\times SAA)}$). The AUC was 0.842 for the MDRO diagnosis using the joint test, which was higher than AUC of the PCT/CRP/SAA single test. The AUC of CRP test was higher than the AUC of the SAA test. More details are shown in **Table 3** and **Figure 1**.

Comparison of the yearly distributions of the MDRO infection strains

The patients with MDRO infections were mainly infected with CRAB and CRE. The comparison of the yearly distributions of the MDRO infection strains showed significant differences (P < 0.05). More details are shown in **Table 4**.

A multivariate logistic regression analysis of the MDRO infection risk factors in COPD patients with pulmonary infections

The multivariate regression analysis identified invasive treatment procedures, long-term bed rest, and increased SAA concentrations as the independent risk factors for MDRO infections in COPD patients with pulmonary infection (all P < 0.001). More details are shown in **Tables 5** and **6**.

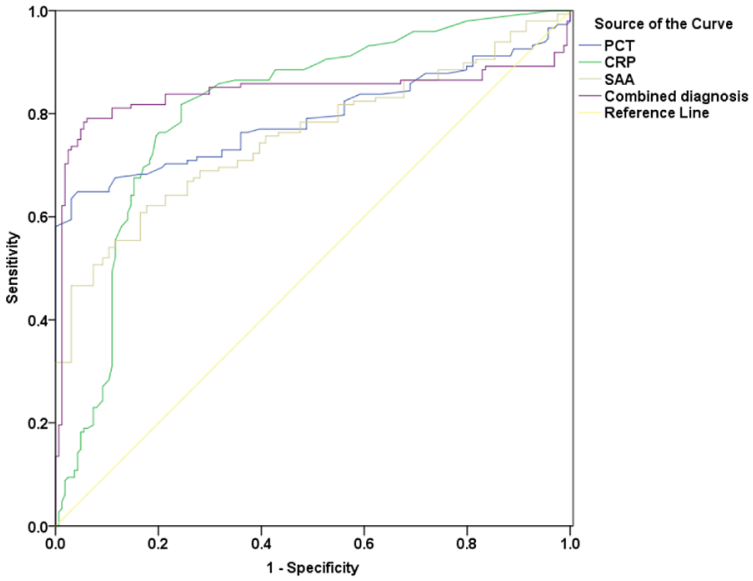

Figure 1. The ROC curve of the infection-related markers for MDRO infections. ROC: receiver operating characteristic. MDRO: multi-drug resistant organisms.

Table 4. Comparison of distribution of the MDRO infection strains in 2017, 2018, and 2019

Index	2017	2018	2019	χ^2	P
CRE	7	3	14	29.083	0.001
CRPA	2	13	3		
CRAB	37	21	16		
CRKP	2	1	1		
MRSA	3	2	1		
VREFm	1	0	1		

Note: CRE: carbapenem-resistant Enterobacteriaceae; CRPA: carbapenem-resistant *Pseudomonas aeruginosa*; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRKP: carbidenes-resistant *Klebsiella pneumoniae*; MRSA: methicillin-resistant staphylococcus aureus; VREFm: vancomycin-resistant *Enterococcus faecium*.

Discussion

Bacterial cultures are still the prevailing gold standard for MDRO diagnosis, but their positive rate is as low as approximately 15%, leading to delayed diagnoses and medication administration for MDRO infections [11]. Patients with MDRO infections are more resistant to antibiotics, so treatment regimens need to be tailored to the specific MDRO infection pathogens to control the disease progression [16-19]. The delay in the diagnosis and effective administration of medication for MDRO infections has a negative impact on patient prognosis. Therefore, clinical research has focused on identifying the relevant markers for the early diagnosis of MDRO infections. The WBC count is the most commonly-used clinical marker for infections, but it fluctuates significantly due to the effects of many factors and is increased in most patients with bacterial infections. In this study, we found increased WBC counts in patients with or without MDRO infections and the two groups were not significantly different, suggesting that the WBC count alone is not effective at diagnosing MDRO infections. So we selected other infection-related markers for further study. CRP, a common test marker, is synthesized in the liver under the mediation of interleukin 6 and other inflammatory factors [20]. CRP concentrations can be increased by infections, oxidative stress, and bodily injuries, so its diagnostic specificity is poor [21, 22]. A previous study found that CRP concentration is positively correlated with the severity of infections [23]. In the present study, the increase in CRP concentrations was more marked in patients with MDRO infections, a possible consequence of the poor treatment efficacy in patients with MDRO infections. PCT is a more specific marker for bacterial infections [24]. An increased PCT concentration indicates the existence of a bacterial infection. In this study, the increase in PCT concentrations was more marked in patients with MDRO infections, suggesting that MDRO infections are severe bacterial infections. SAA is a marker for acute infection, and it is increased in the early stage of MDRO infections and reflects their severity [25]. Here, the SAA concentrations were markedly increased in the patients with MDRO infections, indicating that MDRO infections are more serious than general infections. But the multivariate regression analysis in this study excluded CRP and PCT from the risk factors for MDRO infections, which may be due to the small sample size and the abnormally poor specificity of

Table 5. The independent variables and the assignment of risk factors for MDRO infections in the 278 COPD patients with pulmonary infections

Factors	Independent variable	Assignment
Invasive treatment procedures	X1	Yes = 1, No = 0
Long-term bed rest	X2	Yes = 1, No = 0
PCT	X3	> 0.5 μg/L = 1, ≤ 0.5 μg/L = 0
CRP	X4	> 8 mg/L = 1, ≤ 8 mg/L = 0
SAA	X5	> 10 mg/L = 1, ≤ 10 mg/L = 0

Note: MDRO: multi-drug resistant organisms; PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; COPD: chronic obstructive pulmonary disease.

Table 6. A multivariate logistic regression analysis of the risk factors for MDRO infections in COPD patients with pulmonary infections

Group	β	SE	Wald	OR (95% CI)	P
Invasive treatment procedures	1.567	0.592	12.675	3.235 (2.874-7.634)	< 0.001
Long-term bed rest	1.367	0.489	12.126	2.796 (2.633-7.567)	< 0.001
PCT (μg/L)	0.623	0.209	3.223	2.012 (1.565-3.632)	0.079
CRP (mg/L)	0.089	0.041	0.752	1.079 (0.934-1.034)	0.682
SAA (mg/L)	1.421	0.575	11.456	3.234 (3.002-7.432)	< 0.001

Note: MDRO: multi-drug resistant organisms; PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval.

the two markers for infectious diseases. Here we designed the joint CRP, PCT, and SAA test for the early diagnosis of MDRO infections and noted a higher AUC in the joint test than in any single test. So, the joint test of the three markers is fairly effective at the clinical diagnosis of MDRO infections.

We investigated the distribution of the MDRO infection strains in COPD patients with pulmonary infections and discovered that CRAB and CRE infections were the most prevalent. A previous study also found that CRAB and CRE infections are the main types of MDRO infections in patients in ICUs, which is consistent with the results of this study [26]. We speculate that such consistency may be because most COPD patients with pulmonary infections are critically affected and have bacterial infections similar to those of ICU patients. Studies have shown that the increase in the use of antibiotics has led to a higher risk of MDRO infections [27, 28]. Patients with COPD and pulmonary infections have low immunity, a high risk of infections, and a general need for antibiotics after surgery, which weakens the body defense and facilitates the spread of MDRO strains between patients [29]. CRAB is the most common MDRO strain in the clinic, and it has high drug resistance [30]. The prevention and control of MDRO infections in recent years have caused a decreasing trend in the high incidence of CRAB infections, but the overall incidence of CRE infections is still increasing. Whether this increase is caused by the improper use of antibiotics or by community-acquired infections needs to be further investigated. Also, the related monitoring and management of MDRO infections should be strengthened.

Here we analyzed the risk factors for infections and identified some invasive treatment procedures such as endotracheal intubation and gastric tube intubation, long-term bed rest, and increased SAA concentrations as independent risk factors for MDRO infections in COPD patients with pulmonary infections. Previous studies suggest that COPD patients with pulmonary infections are at a high risk of developing MDRO infections due to their severe systemic symptoms, decreased body defenses, invasive operations, and long-term bed rest, findings consistent with the results of the present study [31, 32].

Here we list some nursing interventions for preventing MDRO infections in COPD patients with pulmonary infections: 1. Nurses should ensure the airways of patients with COPD and pulmonary infections are unobstructed,

because an open airway can facilitate breathing and lung ventilation and reduce the risk of lung infections. 2. Nurses should take measures to promptly stimulate the excretion of sputum in patients, such as making the patients lie in a prone position and patting their backs, sputum suction, and tracheotomy for sputum excretion, because sputum blockage is common in patients with COPD and pulmonary infections and may impair the respiratory function, exacerbate cerebral ischemia and hypoxia, and increase the risk of MDRO infections. 3. Nurses should promptly disinfect the ward daily and disinfect or destroy objects used during the treatment for infected patients.

This study is subject to some limitations. For example, the sample size was small, so we should design a multi-center study to expand the sample size. Moreover, this study did not provide relevant interventions for MDRO infections in COPD patients with pulmonary infections, so we should take interventions to investigate the prevention of MDRO infections.

In summary, the joint CRP, PCT, and SAA test is moderately effective in the early diagnosis of MDRO infections. Invasive treatment procedures, long-term bed rest, and increased SAA concentrations are independent risk factors for MDRO infections in COPD patients with pulmonary infections.

Disclosure of conflict of interest

None.

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