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Original Article

Distribution, diagnosis, and analysis of related risk factors of multidrug-resistant organism in patients with malignant neoplasms

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Abstract: Objective: In this study, we sought to investigate the distribution characteristics, early diagnosis, and related risk factors of multidrug-resistant organism (MDRO) in patients with malignant tumors. Methods: A total of 278 patients with malignant tumors and infections were selected in the Department of Oncology for retrospective study, including 128 MDRO patients and 150 non-MDRO patients. The markers of bacterial culture were detected, and the serum procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA) levels were measured in patients' blood samples. The diagnostic value of PCT, CRP, and SAA for MDRO was evaluated, the distribution of MDRO in different years and different infection sites was analyzed, and the related risk factors of MDRO infection were studied. Results: The PCT, CRP, and SAA in the MDRO group were significantly higher than those of the non-MDRO group (all $P<0.001$). The area under the curve of receiver operating characteristics for the diagnosis of MDRO by PCT, CRP, and SAA. The combination of the three was 0.792, 0.811, 0.755, and 0.842, respectively. The distribution of MDRO strains in different years was statistically different ($P<0.05$), as well as the distribution of MDRO in different infection sites ($P<0.05$). Multivariate regression analysis demonstrated that invasive operation, excessive bed rest, hypoproteinemia, PCT, and SAA were independent risk factors for MDRO infection in patients with malignant tumors (all $P<0.05$). Conclusion: The combination of CRP, PCT, and SAA displays a value for early diagnosis of MDRO infection. MDRO infections in malignant tumors mainly include carbapenem-resistant Acinetobacter baumannii and carbapenem-resistant Escherichia coli. There are differences in terms of MDRO strains in different years and different infection sites, and there are many risk factors regarding MDRO infection in patients with malignant tumors. Intervention should be taken in order to reduce the rate of MDRO infection.

Keywords: Multidrug-resistant organism, inflammatory factors, malignant neoplasms, distribution characteristics, risk factors

Introduction

Due to the invasion of tumor cells and the treatments by radio-chemotherapy, malignant tumor patients have compromised immune systems to protect them from infection. Additionally, the process of treatments, invasive operations, and surgical treatments leads to a high chance of infection by multidrug-resistant organisms (MDRO) [1, 2]. Misuse of clinical antibiotics has increased the number of ICU patients infected by MDRO, which greatly affects the prognosis and life quality of patients [3]. MDRO infections notably escalates the disease progress and the mortality rate [4]. The poor efficacy of antibiotics after MDRO infection impedes the clinical treatment, while it increases the financial burden of patients [5].

Bacterial culture is the gold standard for MDRO diagnosis. However, clinical research has found that the positive rate of bacterial culture was only 15%, which delays the treatment of MDRO patients [6]. Therefore, the early diagnosis of MDRO patients with malignant tumors, the distribution characteristics of the microbiome, and related risk factors are beneficial to the early intervention and prevention of MDRO infection

in patients with malignant tumors. Previous studies have reported the distribution of MDRO microbiome and related risk factors of malignant tumor infection, but research on the early diagnosis of MDRO infection in malignant tumor remains exclusive [7]. Our study aims to investigate the MDRO infection and analyze related infection indicators of patients with malignant tumors at the Traditional Chinese Medical Hospital of Zhuji, so as to provide a clinical reference for the prevention and control of MDRO in patients with malignant tumors.

Materials and methods

Clinical materials

This study was approved by the Ethics Committee of the Traditional Chinese Medical Hospital of Zhuji. A total of 278 patients with malignant tumors and infections admitted to Tra ditional Chinese Medical Hospital of Zhuji from January 2017 to December 2019 were selected for prospective study, including 128 patients with MDRO infection and 150 patients without MDRO. All patients were 23-74 years old, with an average age of 64.8±7.6 years.

Inclusion and exclusion criteria

Inclusion criteria: ① meet the pathological diagnostic criteria for malignant tumors [8]; ② meet the diagnostic criteria for infectious diseases [9]; ③ 18-75 years old; and ④ positive on bacterial culture of blood or urine culture or secretion. Exclusion criteria: ① participants with immunodeficiency and ② participants with multiple bacterial infections.

Methods

Bacterial culture: Infected patients were subjected to collections of blood, urine, and secretions (sputum, pus, pleural or intra-abdominal effusion, etc.) and sent for inspection according to the operation regulations of National Clinical Inspection [10]. The MDRO diagnostic standard was referred to the introduction of MDRO types and diagnostic criteria in Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance, of which common types of MDRO mainly included carbapenem-resistant Escherichia coli (CRECO), carbapenem-resistant Pseudomonas aeruginosa (CRPA), carbapenem-resistant Acinetobacter baumannii (CRAB), carbapenem-resistant Klebsiella pneumoniae (CRKP), methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant Enterococcus faecium (VREFM) [11]. Walk A-way40 automatic microbial identification instrument (Siemens, Japan) was applied for the bacterial analysis.

Blood infection markers: After the infection, two tubes of 5 mL cubital venous blood were collected from each patient, which were stored in sterile tubes of ethylenediaminetetraacetic acid (EDTA) at 4°C for 15 min, followed by the separation of serum and plasma by centrifugation at 1106.8× g and storage at -80°C. The quantification of white blood cells (WBC) was carried out by Coulter LH750 automatic blood cell analyzer (Beckman Coulter Company, USA). The levels of serum procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA) was measured by enzyme-linked immunosorbent assay (ELISA) using automatic immunoassay analyzer (Siemens, Germany).

Outcome measures

PCT, CRP, and SAA levels were measured, and diagnostic values for MDRO by each infection marker or in combination of the three was assessed using the receiver operating characteristic (ROC) curve.

The distribution of MDRO in different years and different infection sites was recorded.

Multivariate logistic regression was applied to analyze risk factors for MDRO infection in patients with malignant tumors.

Statistical analysis

The data was analyzed by SPSS 17.0 statistical software. Continuous variables were presented as mean ± standard deviation ($\bar{x}$ ± sd). If the data was not normally distributed, it was presented as M (P25, P75). When data had a normal distribution with equal variance, it was analyzed by independent-samples t test. If the data was not normally distributed or with unequal variance, it was processed by Mann-Whitney U test, shown as Z. The counting data was analyzed by Pearson Chi-square, presented as χ^2. ROC diagnostic curve was used to evaluate

Table 1. Comparison of general information between two groups of patients

Categories	MDRO infection group (n=128)	Non-MDRO infection group (n=150)	χ^2/t	P
Gender (male:female)	76:52	89:61	0.000	0.994
Age (years)	63.9±9.5	65.1±8.2	1.131	0.259
BMI (kg/m^2)	21.03±3.69	21.16±3.79	0.288	0.773
Infection sites			0.074	0.999
Lung infection	93	110		
Blood infection	16	19		
Urinary tract infection	3	3		
Surgical incision infection	14	16		
Other infection	2	2		
Length of hospitalization (d)	15.9±6.5	10.5±7.9	6.175	<0.001
Fever days (d)	10.5±6.2	7.5±4.4	4.712	<0.001
Invasive operation ratio	91	74	13.556	<0.001
Excessive bed rest (Yes/No)	52/76	35/115	9.604	0.002
Comorbid disease				
Hypoproteinemia	31.26±5.64	33.73±5.69	3.622	<0.001
Hypertension	52	61	0.000	0.994
Type 2 diabetes	54	69	0.407	0.524
Coronary heart disease	41	52	0.215	0.643
Tumor types			1.510	0.993
Colorectal cancer	32	39		
Lung cancer	19	23		
Colon cancer	29	31		
Gastric cancer	19	17		
Bladder Cancer	10	12		
Liver cancer	8	12		
Gallbladder cancer	4	6		
Pancreatic cancer	3	5		
Other cancer	4	5		

Note: BMI: body mass index; MDRO: multidrug-resistant organism.

the value of diagnosis, and multiple variable indicators were combined to establish multiple logistic regression models. Medcalc software was conducted to plot the ROC curve in order to calculate the area under the curve (AUC), which was analyzed by Z test to compare the differences between different ROC curves. MDRO infection was used as the dependent variable to plot multiple logistic regression models. P<0.05 indicated a statistically significant difference.

Results

Comparison of general information between two groups of patients

There was no significant difference between the two groups in gender, age, body mass index (BMI), comorbid disease and hypertension, type 2 diabetes, coronary heart disease, infection sites, and tumor types (P>0.05). The length of hospitalization, fever days, invasive operation ratio, and excessive bed rest ratio were remarkably higher. There were much fewer patients with hypoproteinemia in the MDRO infection group than in non-MDRO group (P< 0.05). See **Table 1**.

Comparison of infection related blood indexes between two groups of patients

The levels of PCT, CRP, and SAA in the MDRO infection group were notably higher than those ~~of~~ in non-MDRO infection group (all P<0.001). ~~t~~There was no statistically significant difference regarding the number of WBC between the two groups (P>0.05). See **Table 2**.

Table 2. Comparison of infection related blood indexes between two groups of patients

Categories	MDRO infection group (n=128)	Non-MDRO infection group (n=150)	t	P
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; WBC: white blood cell; SAA: serum amyloid A; MDRO: multidrug-resistant organism.

The diagnostic value of infection-related blood indexes for MDRO infection

The AUC of the ROC curve for the diagnosis of MDRO by PCT was 0.792. When the PCT was at the cut-off value of 0.765 μg/L, the Youden index was 0.606, the specificity was 0.957, and the sensitivity was 0.649. The AUC of ROC curve for the diagnosis of MDRO by CRP was 0.811. When the CRP was at the cut-off value of 32.145 mg/L, the Youden index was 0.574, the specificity was 0.756, and the sensitivity was 0.818. The AUC of ROC curve for the diagnosis of MDRO by SAA was 0.755. When the SAA was at the cut-off value of 119.623 mg/L, the Youden index was 0.436, the specificity was 0.970, and the sensitivity was 0.466. Logistic regression of the three combined diagnosis to obtain the best diagnosis model equation: Logit (P) = -5.098+7.923*PCT+7.453*CRP+7.346*SAA to establish the probability value of MDRO infection risk, which is the prediction of the probability of disease occurrence based on risk factors $P = +e^{-(-5.098+7.923*PCT+7.453*CRP+7.346*SAA)}$. The AUC of the combined diagnosis of the three indexes was 0.842. See **Table 3** and **Figure 1**.

Comparison of the composition of MDRO strains in different years

MDRO infections in malignant tumors mainly included CRAB and CRECO. The distribution of MDRO strains in different years showed no statistical difference (P<0.05). See **Table 4**.

Comparison of the distribution of MDRO strains in different infection sites

MDRO infections in patients with malignant tumors were mainly dominated by lung, blood, and surgical incision infections. There were no significant differences regarding the distribution of MDRO infections in different sites (P<0.05). See **Table 5**.

Multivariate logistic regression analysis of MDRO infection in patients with malignant tumor

Multivariate regression analysis uncovered that invasive operation, excessive bed rest, hypoproteinemia, PCT and SAA were independent risk factors of MDRO infection in patients with malignant tumors (all P<0.05). See **Tables 6** and **7**.

Discussion

It has been reported that the gold standard for the diagnosis of MDRO is bacterial culture. However, some studies have shown that the positive rate of bacterial culture is about 15%, leading to delays in the diagnosis and therapy of MDRO [6]. Patients with MDRO infection are more resistant to antibiotics, which often requires the treatment of specific pathogens that cause MDRO to control the disease. In addition, delays in the diagnosis and effective treatment will also influence the prognosis [12-15]. Therefore, identification of related infection indicators opens a new door for MDRO diagnosis.

White blood cell (WBC) count is the most used clinical indicator to represent infections, which is, however, affected by many factors and increased in most patients with bacterial infections. In this study, it revealed that WBC count is increased in both MDRO and non-MDRO patients and there is no statistically significant difference between the two groups, which suggests that WBC alone is not effective in identifying MDRO infection. Thus, it is necessary to find other infection-related indicators for further study. C-reactive protein (CRP) is synthesized in the liver in response to interleukin 6 (IL-6) and other inflammatory factors, which is commonly used as a clinical indicator [16]. However, clinical studies have found that CRP is not only upregulated by infection, but increased during oxidative stress or body injury [17, 18], indicating its poor specificity to diagnose infections, whereas other studies have shown a positive correlation between CRP and the se-

Table 3. Comparison of PCT, CRP and SAA in predicting AUC of MDRO infection

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

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

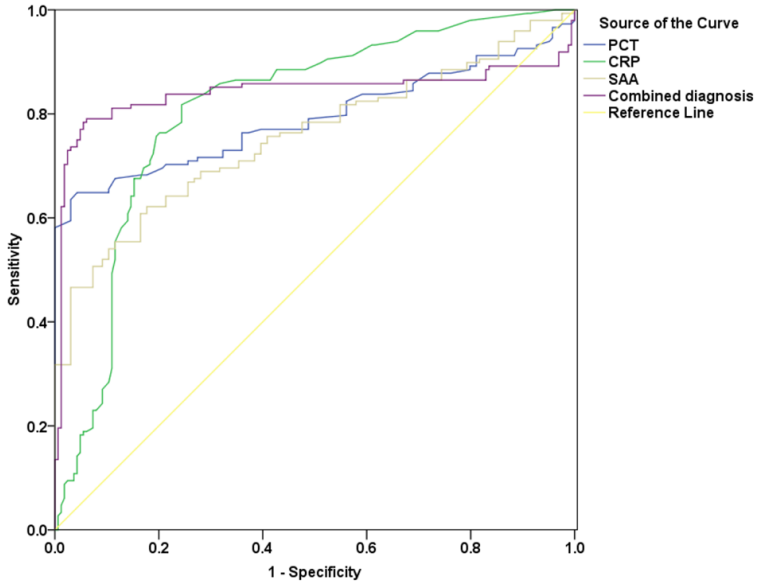

Figure 1. ROC curve of infection-related blood indexes for MDRO infection. PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; ROC: receiver operating characteristic.

Table 4. Comparison of the composition of MDRO strains in different years

Categories	2017	2018	2019	χ^2	P
CRECO	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: CRECO: carbapenem-resistant Escherichia coli; CRPA: carbapenem-resistant Pseudomonas aeruginosa; CRAB: carbapenem-resistant Acinetobacter baumannii; CRKP: carbapenem-resistant Klebsiella pneumoniae; MRSA: methicillin-resistant Staphylococcus aureus; VREFM: vancomycin-resistant Enterococcus faecium; MDRO: multidrug-resistant organism.

verity of infection [19]. Our results demonstrated that CRP is notably upregulated in patients with MDRO infection, which may be correlated to the poor treatment of MDRO infection.

Procalcitonin (PCT) is a relative specific indicator of bacterial infection, so the upregulation of PCT indicates the bacterial infection [20]. Our data shows remarkable upregulation of PCT after MDRO infection, suggesting that MDRO infection is severe bacterial infection. Serum amyloid A (SAA) is an indicator of acute infection, which is increased in the early stage of MDRO infection and is also one of the indicators showing the severity of the infection [21]. In this study, patients with MDRO infection have notably upregulated SAA, which unveils that MDRO infection is more severe than normal infections. We further investigated the combination of CRP, PCT, and SAA for early diagnosis of MDRO infection, which demonstrated that AUC value of the combined diagnosis of the three was higher than using single indicator, suggesting the clinical value by using the combination of these three for the diagnosis of MDRO infection.

By analyzing the distribution of MDRO strains in infected patients, our results uncovered that patients with malignant tumors were mainly infected with carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Escherichia coli* (CRECO). Previous studies have found that MDRO infections of patients in intensive care units (ICU) mainly included CRAB and CRECO, which consistent with our results, possibly due to the fact that most

Table 5. Comparison of the distribution of MDRO strains in different infection sites

Categories	Lung infection	Blood infection	Urinary tract infection	Incision infection	Other infection	χ^2/F	P
CRECO	16	6	0	1	1	32.227	0.041
CRPA	16	1	0	1	0		
CRAB	56	7	2	8	1		
CRKP	2	1	1	0	0		
MRSA	2	1	0	3	0		
VREFM	1	0	0	1	0		

Note: CRECO: carbapenem-resistant Escherichia coli; CRPA: carbapenem-resistant Pseudomonas aeruginosa; CRAB: carbapenem-resistant Acinetobacter baumannii; CRKP: carbapenem-resistant Klebsiella pneumoniae; MRSA: methicillin-resistant Staphylococcus aureus; VREFM: vancomycin-resistant Enterococcus faecium; MDRO: multidrug-resistant organism.

Table 6. Independent variable-outcome table of risk factors of MDRO infection in 278 patients with malignant tumor

Factors	Independent variable	Outcome
Length of hospitalization	X1	≥15=1, <15=0
Fever days	X2	≥10=1, <10=0
Invasive operation	X4	Yes=1, No=0
Excessive bed rest	X5	Yes=1, No=0
Hypoproteinemia	X6	≤30 g/L=1, >30 g/L=0
PCT	X7	>0.5 μg/L=1, ≤0.5 μg/L=0
CRP	X8	>8 mg/L=1, ≤8 mg/L=0
SAA	X9	>10 mg/L=1, ≤10 mg/L=0

Note: PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; MDRO: multidrug-resistant organism.

of the patients with malignant tumors were critically ill whose infection are similar to ICU patients [22]. Previous studies have also reported that the increase MDRO infections were due to increased use of antibiotics [23, 24]. Patients with malignant tumors undergoing radio-chemotherapy have compromised immunitiesy and are susceptible to infection, or after surgery, antibiotics are usually used for treatment, and patients with malignant tumors were more vulnerable than normal patients, which makes MDRO strains spread easily among patients [25]. CRAB is the most common MDRO strain clinically, which is high drug-resistant, in recent years, with the development of MDRO infection control, although CRAB has a high incidence, whose trend is decreased, while CRECO shows an increasing trend [26]. Whether this is correlated with the misuse of antibiotics and the community infections, further investigations are needed to enhance the supervision and management. This study also further investigated that there are some differences in terms of MDRO infections in different sites. Malignant tumor patients undergo invasive operations, which may be correlated with MDRO infections in different parts. Thus, when performing invasive operations, timely operation according to the standard protocol is of necessity [27].

Domestic studies have shown that patients with malignant tumors with excessive bed rest, invasive operations, combined and long-term use of antibiotics, and hypoproteinemia are more likely to be infected by MDRO [7]. Our data revealed that multivariate regression analysis of MDRO infection in patients with malignant tumors demonstrated that invasive operations, extensive rest, hypoproteinemia, PCT, and SAA were independent risk factors of MDRO infection in patients with malignant tumors, which is consistent with the previous findings.

Caveat and future work: our work was a retrospective study but had a lack of prospective research. The sample size in this study was small, so multi-center research should be further conducted to expand the sample size. Our study did not focus on MDRO related interventions. tTherefore, further intervention measures should be carried out to investigate prevention strategies of MDRO infection.

In summary, the combination of CRP, PCT, and SAA is valuable for the early diagnosis of MDRO infection. The MDRO in malignant tumors mainly include CRAB and CRECO infections. There are differences regarding MDRO strains at different infection sites. Invasive operation,

Table 7. Multivariate logistic regression analysis of MDRO infection in patients with malignant tumor

Factors	β	SE	Wald value	OR value (95% CI)	P
Length of hospitalization (d)	0.098	0.034	0.821	1.132 (0.957-1.432)	0.687
Fever days (d)	0.069	0.029	0.712	1.019 (0.978-1.081)	0.715
Invasive operation	1.421	0.571	12.439	3.123 (2.931-7.565)	<0.001
Excessive bed rest	1.234	0.413	11.214	2.841 (2.741-7.123)	<0.001
Hypoproteinemia	0.867	0.262	4.172	2.164 (1.278-3.732)	0.038
PCT	0.906	0.269	4.165	2.164 (1.315-3.743)	0.022
CRP (mg/L)	0.071	0.038	0.714	1.016 (0.958-1.074)	0.721
SAA (mg/L)	1.393	0.542	11.378	3.145 (2.938-7.465)	<0.001

Note: PCT: procalcitonin; CRP: C-reactive protein; SAA: serum amyloid A; MDRO: multidrug-resistant organism.

excessive bed rest, hypoproteinemia, PCT, and SAA are independent risk factors of MDRO infection in patients with malignant tumors. Corresponding interventions should be taken early to reduce the rate of MDRO infection in patients with malignant tumors.

Disclosure of conflict of interest

None.

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