Infection with multi-drug resistant organisms in patients with limb fractures: Analysis of risk factors and pathogens

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Received March 20, 2023; Accepted October 17, 2023

DOI: 10.3892/br.2023.1716

Abstract. Infection with multi-drug resistant organisms (MDROs) has emerged as a global problem in medical institutions. Overuse of antibiotics is the main cause of drug resistance. Notably, the incidence of infection with MDROs increases in patients with limb fractures who have undergone invasive surgery. The present study aimed to analyze the risk factors for postoperative MDROs infection in a cohort of patients with limb fractures. A retrospective study was performed on the data of patients with fractures between January 2020 and August 2022. Postoperative surgical site infection occurred in 114 patients in total, of which 47 were infected with MDROs. Univariate logistic regression analysis and multivariate binary logistic regression were used to confirm the associations between independent risk factors and MDRO infection. A total of 155 bacteria were collected from patients with MDROs infection and patients with non-MDROs infection, of which 66.5% were gram-positive bacteria and 33.5% were gram-negative. *Staphylococcus aureus* accounted for 26.5% of the 155 pathogens. MDROs, such as methicillin-resistant *S. aureus* and extended-spectrum β-lactamases-positive gram-negative bacillus, were detected after antibiotic treatment. Univariate analysis indicated that the number of antibiotics administered, being bedridden, repeat infection, operative time and repeated operation were different in the two groups. In addition, univariate logistic analysis indicated that being bedridden (OR, 3.98; P=0.001), administration of >2 antibiotics (OR, 2.42; P=0.026), an operative time of >3 h (OR, 3.37; P=0.003), repeated infection (OR, 3.08; P=0.009) and repetition of procedures (OR, 2.25; P=0.039) were individual risk factors for MDRO infection. Multivariate analysis showed that being bedridden (OR, 2.66; P=0.037), repeated infection (OR, 4.00; P=0.005) and an operative time of >3 h (OR, 2.28; P=0.023) were risk factors of MDRO infection. In conclusion, constrained antibiotic use, shortened operative time and increased activity duration can effectively prevent surgical-site infection with MDROs in patients with fractures.

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Key words: multi-drug resistant organisms, limb, fracture, orthopedic surgery, bedridden

Introduction

Fracture is the most common form of orthopedic trauma and has a high global incidence. The prevention and treatment of bacterial infection are important post-operation in patients with fractures (1). Antibiotics can effectively suppress infection by inhibiting bacterial growth; however, bacteria can become resistant to antibiotics after simultaneous multi-antibiotic therapy. Multi-drug resistant organisms (MDROs) are characterized by resistance to at least three antibiotics and infections with these organisms are difficult to treat (2). The occurrence of fracture-related infection often depends on the site of injury, surgical incision size and open wounds. Although the majority of studies on fracture-related infections have largely identified reliable risk factors involved in the surgical and recovery processes (1,3), little attention has been paid to MDROs infection in patients with fractures. Notably, MDROs infection often results in a worse outcome compared with infections with non-resistant pathogens. Patients who suffer from multidrug-resistant pathogens have been reported to exhibit a 3-fold increase in amputation (4,5). Recent research has indicated that infections occurring in limb fractures account for 80% of whole fracture-related infection cases, and bones of the extremities are more likely to be infected with common MDROs, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamases (ESBLs) (+) *Escherichia coli* (6,7), suggesting that bones of the extremities are more susceptible to MDROs infection. For patients with fractures, effective empirical antibiotic treatment is vital in the early periods. It has previously been indicated that effective antibiotic use can greatly raise sensitivity and avoid resistance (8). In addition, eligible methods of pathogen prevention can inhibit nosocomial infections (9). Nevertheless, research on the prevalence of MDROs and the risk of MDROs infection is still rare. To explore the epidemiology and drug resistance of MDROs, and to discover the factors associated with MDROs infection in patients with limb fractures, the present study collected information on limb fracture cases, including age, sex, injury sites, operative records, pathogens and drug resistance, and provided evidence for clinical antibiotic treatment and pathogen prevention.

Patients and methods

Data collection. The present study collected the medical records of patients treated at Bayi Orthopedic Hospital

Table I. Demographic and clinical characteristics of the 114 patients with limb fractures.

Demographic characteristic	Value
Mean ± SD age, years	48.25±15.18
Sex, male/female (%)	91 (79.8)/23 (20.2)
Fracture sites, n (%)	
Upper limb	
Radius and ulna	2 (1.8)
Humerus	4 (3.5)
Hand	36 (31.5)
Multiple fracture	5 (4.4)
Lower limb	
Femur	9 (7.9)
Tibia and fibula	20 (17.5)
Patella	4 (3.5)
Foot	28 (24.6)
Multiple fracture	5 (4.4)
Upper and lower	1 (0.9)
Cause of injury, n (%)	
Mechanical	38 (33.3)
Fall	27 (23.7)
Traffic	18 (15.8)
Bruise	14 (12.3)
Others	17 (14.9)
Clinical characteristics	
Mean ± SD length of hospital stay, days	19.2±11.8
Mean ± SD hemoglobin, g/l	130.1±19.2
Mean ± SD albumin, g/l	39.2±3.67
Diabetes, n (%)	13 (11.4)
Infectious pathogens, n (%)	
1 strain	85 (74.5)
2 strains	19 (16.7)
>2 strains	10 (8.8)
Operative grade, n (%)	
I	1 (0.9)
II	10 (8.8)
III	77 (67.5)
IV	26 (22.8)
Incision type, n (%)	
I	18 (15.8)
II	45 (39.5)
III	51 (44.7)

Table II. Resistance of multi-drug resistant gram-positive bacteria.

Antimicrobial	*Staphylococcus aureus* (%)
Gentamicin	5.88
Ceftriaxone	94.12
Ampicillin/Sulbactam	94.12
Amoxicillin/Clavulanate potassium	100.00
Oxacillin	94.12
Penicillin	94.12
Vancomycin	0.00
Clindamycin	82.35
Erythromycin	94.12
Ciprofloxacin	94.12
Levofloxacin	23.53
Tetracycline	11.76
Rifampin	29.41
PCST	35.29
Cefoxitin	5.88
Moxifloxacin	5.88
Linezolid	0.00
Synercid	5.88

PCST, Pediatric Compound Sulfamethoxazole Tablets.

(Chengdu, China) between January 2020 and August 2022. The information was obtained from the electronic medical record system, and included sex, age, albumin levels, hemoglobin levels, diabetes diagnosis, length of hospital stay, operative time, antibiotic use, open fracture, repeated infection, whether patients were bedridden, operative grade, fracture sites, implantation materials, injury factors, incision type, surgical approach, body mass index (BMI) and repetition of procedures. The inclusion criteria were as follows: i) Patients diagnosed with a limb fracture; ii) infection occurred after orthopedic surgery; iii) bacteria cultured from the wound discharge (10). The exclusion criteria were: i) Incomplete medical records; ii) fracture at other sites; iii) preoperative infection. VITEK 2 Compact (bioMérieux) automatic microbial analysis system and Microbiology Conventional Panel MicroScan Negative Urine Combo 61 For MicroScan Analyzers 20 Panels (cat. no. B1017-414; Beckman Coulter, Inc.) were used for strain identification and antimicrobial susceptibility testing. S. aureus [American Type Culture Collection (ATCC) 25923], *E. coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) (purchased from ATCC)were used for quality control.

Patients were considered bedridden if they were unable to move or if they remained in bed for >2 weeks, according to clinical need. Operative grade was scored as follows: I, uncomplicated, low risk; II, uncomplicated, medium risk; III, complicated, relatively high risk; IV, quite complicated, high risk. Incision type was scored as follows: I, low infection risk; II, medium infection risk; III, high infection risk.

Statistical analysis. SPSS 26.0 software (IBM Corp.) was used for statistical analysis. The Kolmogorov-Smirnov test was used to assess normality. Normally distributed data are presented as the mean ± standard deviation and Student's t-test was performed to compare group differences. Non-normally distributed data are presented as median (Q1, Q3) and comparisons between groups were made using Mann-Whitney U test. Categorical data are presented as the number of cases and comparisons between the different groups were made using the χ^2 test. Binary logistic regression was used to perform

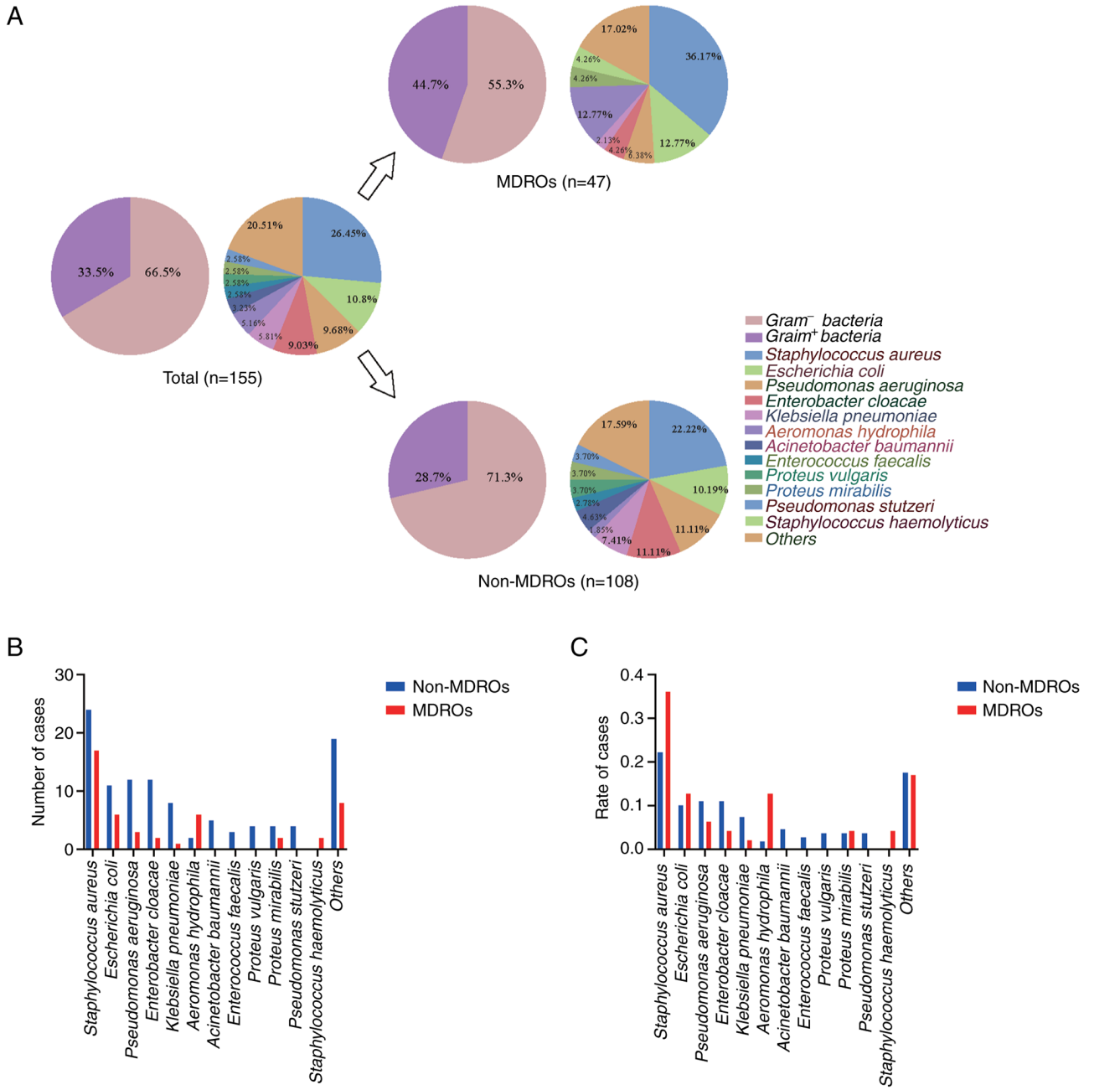

Figure 1. Bacterial infection in patients with limb fractures. (A) Overall distribution of bacteria in the MDROs group and the non-MDROs group. The (B) number and (C) proportion of each bacterial infection in the two groups. MDRO, multi-drug resistant organism.

univariate and multivariate analyses. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 114 patients with limb fractures who suffered from infections were included in the present study. The 114 patients were divided into two groups: The MDRO group (47 cases, including 39 men and 8 women) and the non-MDRO group (67 cases, including 52 men and 15 women). The patients had a mean age of 48.25±15.18 years, 91 (79.8%) were men and a subset of 13 (11.4%) presented with diabetes. Among the 114 patients, 47 (41.2%) had upper limb fractures, 66 (57.9%) had lower limb fractures and one (0.9%) had multiple fractures. Mechanical injury (38 cases, 33.3%) and fall (27 cases, 23.6%) were the main causes of fractures. More details of patient characteristics are presented in Table I. A total of 155 bacteria were cultured from the 114 patients, of which 47 (41.2%) were infected with MDROs. Among the 155 microorganisms, 52 (33.5%) were gram-positive bacteria. A total of 85 (74.6%) patients were infected with only one strain and 29 (25.4%) were infected with multiple pathogens simultaneously. *Klebsiella pneumonia*, *P. aeruginosa*, *Enterobacter cloacae* and *Proteusbacillus vulgaris* infections occurred in combination with each other in the MDROs group (Table SI). Bacteria distributions are shown in Fig. 1A. There were differences in the gram-positive bacteria rate between multi-drug resistant pathogens and non-resistant pathogens. The MDROs

Table III. Resistance of multi-drug resistant gram-negative bacteria.

Antimicrobial	*Escherichia coli* (%)	*Aeromonas hydrophila* (%)	*Pseudomonas aeruginosa* (%)
Amikacin	0.00	0.00	33.33
Gentamicin	66.67	0.00	33.33
Tobramycin	66.67	-	0.00
Cefazolin	100.00	100.00	-
Cefoxitin	16.67	50.00	-
Cefuroxime	100.00	16.67	-
Ceftriaxone	100.00	16.67	-
Ceftazidime	100.00	16.67	100.00
Cefotaxime	100.00	16.67	-
Cefepime	100.00	0.00	100.00
Imipenem	0.00	-	66.67
Meropenem	0.00	66.67	0.00
Aztreonam	100.00	0.00	100.00
Ampicillin/Sulbactam	100.00	100.00	-
Ampicillin	100.00	-	-
Piperacillin/Tazobactam	0.00	100.00	100.00
Ciprofloxacin	83.33	16.67	0.00
Levofloxacin	83.33	0.00	0.00
PCST	83.33	16.67	-
Ertapenem	0.00	83.33	-
Tigecycline	0.00	0.00	-

PCST, Pediatric Compound Sulfamethoxazole Tablets.

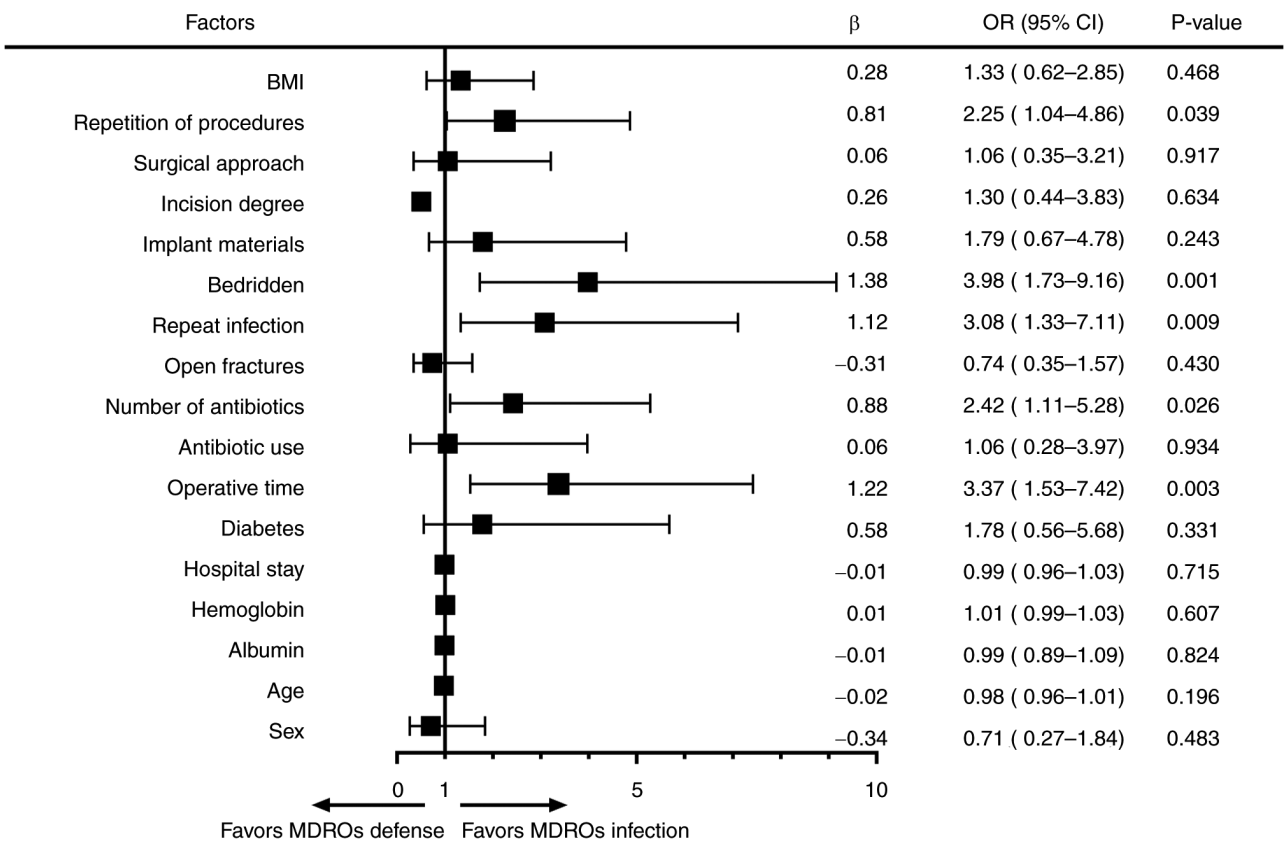

Figure 2. Univariate logistic regression analysis of MDROs infection. BMI, body mass index; MDROs, multi-drug resistant organisms.

Table IV. Univariate analysis of MDRO infection.

Factor	Non-MDRO group	MDRO group	P-value
Sex			0.482
Male	52	39	
Female	15	8	
Mean ± SD age, years	51.3±12.0	46.0±14.7	0.196
Mean ± SD albumin, g/l	39.2±3.5	39.1±4.0	0.826
Mean ± SD hemoglobin, g/l	129.4±20	131.7±16.8	0.610
Median hospital stay (Q1, Q3), days	15 (12, 24)	13 (9, 25)	0.327
Diabetes			0.326
Yes	6	7	
No	61	40	
Operative time			0.002
≥3 h	18	26	
<3 h	49	21	
Antibiotic use			0.934
Yes	61	43	
No	6	4	
Number of antibiotics			0.025
0-2	48	24	
3+	19	23	
Open fractures			0.430
Yes	42	26	
No	25	21	
Repeat infection			0.007
Yes	13	20	
No	54	27	
Bedridden			0.001
Yes	14	23	
No	53	24	
Implant materials			0.239
Yes	51	40	
No	16	7	
Incision degree			0.086
I	10	8	
II	32	13	
III	25	26	
Surgical approach			0.917
Percutaneous	9	6	
Open	58	41	
Repetition of procedures			0.038
Yes	31	31	
No	36	16	
BMI			0.467
≥25	24	20	
<25	43	27	

BMI, body mass index; MDRO, multi-drug resistant organism.

infection group had a higher rate of gram-positive bacterial infections. The comparison of each bacterial strain between the MDROs group and the non-MDROs group is shown in Fig. 1B and C. Bacteria, such as *Aeromonas hydrophila* and

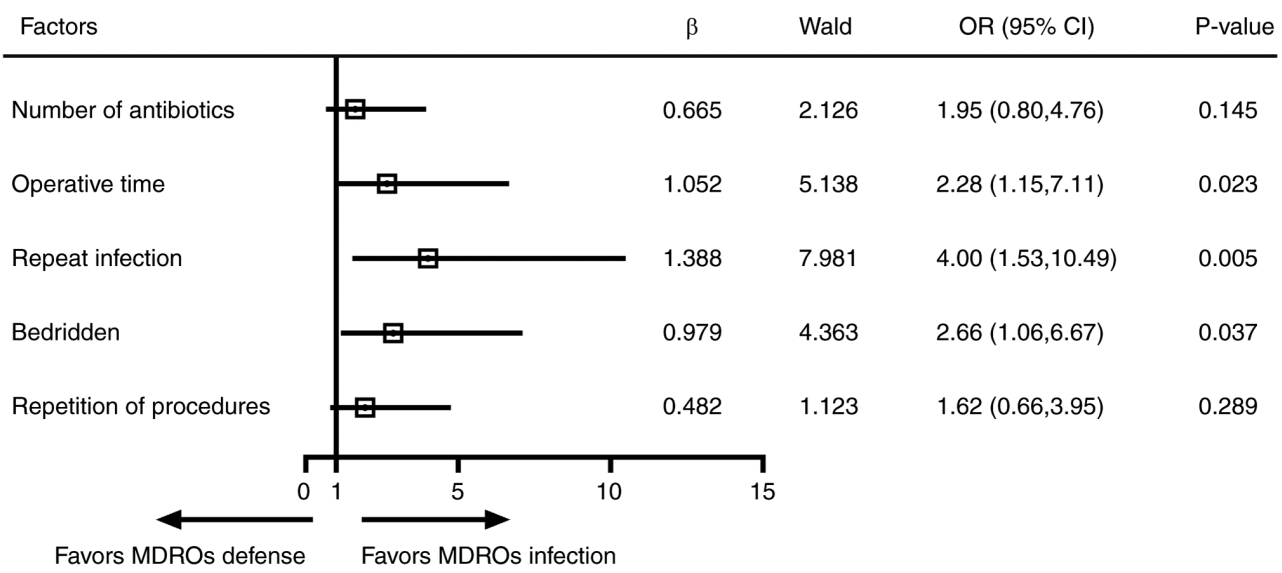

Figure 3. Multivariate logistic regression analysis of MDROs infection. MDROs, multi-drug resistant organisms.

Acinetobacter baumannii, only appeared in the non-MDROs infection group (Fig. 1B). In addition, *S. aureus* was more frequently detected in the MDROs group (Fig. 1C). In the present study, *S. aureus*, a common microorganism that usually causes nosocomial infections (3), was more likely to be resistant to antibiotics. MRSA was the main pathogen of gram-positive MDROs infection cases. Gram-negative pathogens, such as *E. coli* and *A. hydrophila* also exhibited a high level of occurrence in the MDROs group. MIC results of MDROs samples are summarized in Tables II and III. As for gram-positive *S. aureus*, resistance mainly focused on penicillins, erythromycin and lincomycins. Gram-negative bacilli, such as *E. coli* and *K. pneumoniae*, produce ESBLs to hydrolyze antibiotics and thus become insensitive to cephalosporins. The clinical records of antibiotic use were collected to analyze whether drug resistance occurred after an antibiotic treatment. Clindamycin treatment may induce high resistance in *S. aureus*. Gentamicin and vancomycin are still effective methods to prevent those kinds of pathogens (Table SII). Moreover, ESBLs (+) bacteria, such as *E. coli*, *K. pneumoniae* and *P. vulgaris*, accounted for almost half of the gram-negative MDROs that exhibited resistance after prolonged cephalosporin use (Table SII). In summary, the results of the present study demonstrated that bacteria varied in drug resistance during antibiotic therapy.

Univariate analysis of MDROs infection. Univariate analysis was used to assess differences between the two groups. Being bedridden, administration of >2 antibiotics, operative time >3 h, repeated infection and repetition of procedures were closely associated with MDROs infection (Table IV). Univariate logistic analysis was also used to assess the hazard rate of each factor (Fig. 2). Being bedridden (OR, 3.98; P=0.001), administration of >2 antibiotics (OR, 2.42; P=0.026), operative time >3 h (OR, 3.37; P=0.003), repeated infection (OR, 3.08; P=0.009) and repetition of procedures (OR, 2.25, P=0.039) were identified as individual factors that may be associated with MDRO infection.

Multivariate analysis of MDROs infection. To validate the association between the aforementioned significant factors and MDROs infection, multivariate binary logistic analysis was conducted. The results showed that being bedridden (OR, 2.66; P=0.037), repeated infection (OR, 4.00; P=0.005) and operative time >3 h (OR, 2.28; P=0.023) were significant factors associated with MDROs infection (Fig. 3).

Discussion

Pathogens often colonize patients during orthopedic surgery and recovery periods. Infection prevention is of great importance to accelerate postoperative wound healing for patients with fractures. Notably, inappropriate antimicrobial therapy can facilitate bacterial resistance to drugs; MDROs can appear after antibiotic use and have become a challenge to clinical treatment and nursing (11,12). An anti-MDROs strategy is required for pathogen defense. A study in the southwestern and northeastern regions of China found that among all patients with fractures, those with limb fractures have the highest likelihood of developing infections (3). Furthermore, *S. aureus* and *E. coli* were responsible for almost one-third of pathogens (1,3). Similarly, the present study reported that *S. aureus* and *E. coli* were major bacteria in cases of limb infection. Furthermore, the majority of cases of MDRO infection appeared to occur following corresponding antibiotic treatment, suggesting that drug resistance mainly results from antibiotic therapy. Perioperative use of antibacterial drugs is an effective method of infection prevention (13). The present study found no significant difference in antibiotic use between the two groups; however, administration of three or more antibiotics increased the incidence of MDROs infection. Antibiotics are the main cause of pathogen resistance. Patients can suffer from repeated infection as a result of failed control of pathogens in the early phase, and supplemental and prolonged antibiotic therapy can eventually cause bacterial resistance. It has been reported that, following lower extremity surgery, a high proportion of patients undergo amputation after infection

with multi-drug resistant pathogens (4,5). Multidrug-resistant pathogens colonize the wound area and can invade the bloodstream to cause bacteremia. In addition, the occurrence of necrosis near the unhealed wound can lead to amputation (5).

It is well known that patients with low immunity have an increased chance of infection with microbes, including MDROs. Previous research has revealed that low albumin and hemoglobin levels, often considered as evidence of low immunity, are risk factors for clinical infection (14,15). However, the results of the present study did not identify low albumin and hemoglobin levels as risk factors for MDROs infection. Diabetes, a metabolic disorder characterized by an injured immune system, has long been reported to be associated with MDROs infection (16,17). Previous studies have reported that patients with a higher BMI are more likely to suffer from wound infection (18,19). In obese patients, metabolic disturbances can lead to chronic tissue inflammation, and impaired adaptive and innate immunity (20). Nevertheless, there is no evidence in the present study supporting the relationship between diabetes or BMI and MDROs infection. Therefore, a large cohort survey is required to verify this. Notably, being bedridden has been shown to be associated with pulmonary infection in elderly patients with hip fractures, and this was also closely related with MDROs infection in the present study (21). Being bedridden may cause malnutrition, which decreases immune defense. In addition, a lack of movement constrains the blood circulation to the injured site, especially in patients with limb fracture; hypoxia in the affected extremity can increase susceptibility to microbial invasion (22,23).

Prolonged operative time has been reported to increase morbidity in multiple injuries, such as in tibial plateau fractures (24-26). The present study demonstrated that ≥3 h of operative procedures may increase the risk of MDROs infection. Long procedures often result in heavy damage and incisions exposed to the air can promote environmental bacterial colonization. A longer surgical time not only increases the risk of infection but also inevitably increases the possibility of MDROs infections. The subjects included in the present study were all patients with post-operative infection. Notably, the current study also revealed that patients that underwent more than two operations exhibited a higher risk for MDROs infection, suggesting that primary infection happens during a surgical procedure. The present results are insufficient to demonstrate the relationship between incision size and drug-resistant bacterial infection. Further research should record incision size in line with corresponding operative methods. Hospital stay has long been hypothesized to affect wound healing. Prolonged hospital stay can increase nosocomial infection risk, especially in postoperative patients (27,28). However, in the present study, length of hospital stay did not seem to affect the incidence of MDROs infection. The present study also analyzed implanted materials and surgical approaches, and it showed that implanted materials or open surgical modes were not related to MDROs infection, even though they were thought to have a significant role in previous studies (29,30).

Although it has been reported that elderly patients have a higher occurrence rate of MDROs infection (31), there was no significant difference between the mean ages of the two groups in the present study. Regional social structure may explain this discrepancy. Finally, binary logistic regression analysis was performed to assess the five factors that were revealed to be significant in MDROs infection. Three of them were of importance in the prevention of MDROs infection; in conclusion, shortened operative time, improved early pathogen defense and activities in the affected limb may be helpful to decrease MDROs invasion.

The main limitation of the present study was a restricted sample size. In addition, the medical records are limited to one center. A multi-center survey and additional patient records are required in future studies. Besides, the records included in the present study are not detailed enough. The present study also failed to incorporate the changes in bacterial infection before and after antibiotic usage, which is of significant importance in developing antibiotic treatment strategies for MDROs-infected patients. Including confounding factors, such as the pre-admission medical conditions, in the analysis may also enhance the reliability of the study results. The risk factors identified in the present study should be appropriately applied in the prevention of clinical infection. This includes the care of long-term bedridden patients and strict measures to avoid excessively prolonged surgical procedures. Furthermore, infections caused by different MDROs may present variations in infection characteristics, treatment and prognosis. A comprehensive assessment of the impact of different MDROs on infections in patients with limb fractures should be conducted, and tailored intervention strategies should be developed.

Acknowledgements

Not applicable.

Funding

The present study was funded by Chengdu Municipal Health Commission (grant no. 2022100).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JJ led and designed the project. HS, MZ and DD collected data. HS performed the data analysis and statistical analysis. HS interpreted the data and wrote the manuscript. All authors contributed to the article, and read and approved the final manuscript. HS and JJ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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