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Treatment options and clinical outcomes for carbapenem-resistant *Enterobacteriaceae* bloodstream infection in a Chinese university hospital

Chen Li[a,1], Yi Li[b,1], Zhichang Zhao[c], Qing Liu[a], Bin Li[d,*]

[a] Department of Infectious Disease, Fujian Medical University Union Hospital, Fuzhou, Fujian, 350001, China
[b] Department of Clinical Laboratory, Henan Provincial People's Hospital, Zhengzhou, Henan, 450003, China
[c] Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou, Fujian, 350001, China
[d] Department of Clinical Laboratory, Fujian Medical University Union Hospital, Fuzhou, Fujian, 350004, China

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ABSTRACT

Background: Carbapenem resistant *Enterobacteriaceae* (CRE) has become a serious public health problem. Limited information is available about the treatment options that physicians used to fight CRE infections and related clinical outcomes in China. The aim of the present study was to explore the treatment options and clinical outcomes of patients with CRE bloodstream infection (BSI) in a Chinese teaching hospital.
Methods: A retrospective study was conducted during 2011 to 2015 in one Chinese teaching hospital. Demographic, microbiological and clinical characteristics of enrolled subjects were collected from medical records. Data were analyzed by Kaplan–Meier graphs, log-rank test, and Cox regression.
Results: A total of 98 inpatients with CRE BSI were enrolled in this study. For empirical therapy, 26 patients (26.5%) received at least one active drug within 48 h after the onset of bacteremia. For definitive treatment, 59.2% (49/82) patients received at least one active drug and 40.2% (33/82) patients received therapy with no active drug. The overall 30-day mortality was 53.1% (52/98). Adverse outcome appeared to be more likely among patients with previous carbapenem exposure, neutropenia, severity of septic and time to initiation of BSIs. There was no significant difference in the mortality between the two groups of patients with combination therapy versus monotherapy ($p = 0.105$). Severity of sepsis and neutropenia were identified as independent predictors of mortality.
Conclusions: Our study demonstrated a high mortality associated with CRE BSI and a high percentage of inappropriate empirical treatment for CRE BSI patients in a Chinese teaching hospital. Particular attention should be given to the patients with CRE BSI.

Background

Carbapenem resistant *Enterobacteriaceae* (CRE) has become a serious public health problem worldwide. Until now, there are limited treatment options available for CRE infections because these bacteria may exhibit multi-resistance to many important antibiotics, such as β-lactams, aminoglycosides and fluoroquinolones [1,2]. For the dearth of therapeutic options, CRE infections pose additional difficulties in the patients' management and become to be life-threatening. Clinical outcomes of CRE infection are now known to be poor. CRE infections are usually associated with longer length of hospital stay and increased mortality compared with carbapenem susceptible organisms [3–5]. Many reports demonstrated different kinds of treatment options for CRE infections, and combination antimicrobial therapy was thought to probably have a survival benefit to patients when compared with monotherapy [6–9].

In China, the prevalence of CRE is increasing recently for the wide-use of the carbapenem. CHINET data demonstrated that the prevalence of imipenem resistant *Klebsiella pneumoniae* was about 3.0% in 2005, the resistance rose to 9.2% in 2010 and reached

Abbreviations: CRE, carbapenem resistant *Enterobacteriaceae*; BSI, bloodstream infection; HR, hazards ratio; CI, confidence interval.

* Corresponding author at: Department of Clinical Laboratory, Fujian Medical University Union Hospital, 29 Xinquan Rd. Fuzhou, Fujian, 350001, China.
E-mail addresses: lee1230chen@126.com (C. Li), liyi7209@163.com (Y. Li), slip2046@126.com (Z. Zhao), liuqfj@qq.com (Q. Liu), leonlee307@hotmail.com (B. Li).

[1] These authors contributed equally to this study.

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Table 1
Univariate analysis of factors associated with all-cause 30-day mortality of 98 patients with CRE bloodstream infections.

	Results for patients who:		P
	Survived (n = 46)	Died (n = 52)	
Age, mean year (SD)	47.93 (27.5)	46.78 (21.7)	0.818
Gender, no. (%)			
Male	33 (48.5)	35 (51.5)	0.635
Female	13 (43.3)	17 (56. 7)	
Length of stay in hospital (SD)	43.8 (35.8)	32.19 (22.5)	0.055
Ward at onset of BSI, no. (%)			
ICU	18 (45.0)	22 (55.0)	0.749
Non-ICU	28 (48.3)	30 (51.7)	
Time to initiation of BSI (SD)	16.35 (14.5)	23.77 (20.7)	0.045
Polymicrobial BSI, no. (%)			0.294
Yes	14 (38.9)	22 (61.1)	
No	32 (51.6)	30 (48.4)	
Previous carbapenem exposures, no. (%)			
Yes	21 (32.8)	43 (67.2)	<0.001
No	25 (73.5)	9 (26.5)	
Neutropenia, no. (%)			0.005
Yes	12 (30.0)	28 (70.0)	
No	34 (58.6)	24 (41.4)	
Severity of sepsis, no. (%)			<0.001
Sepsis	33 (75.0)	11 (25.0)	
Severe sepsis	5 (19.2)	21 (80.8)	
Septic shock	8 (28.6)	20 (71.4)	
Time to initiation of at least 1 active drug, no. (%)			0.830
>48h	17 (50.0)	17 (50.0)	
≤48h	7 (46.7)	8 (53.3)	
Empirical treatment, no. (%)			0.142
No active drug	37 (51.4)	35 (48.6)	
At least 1 active drug	9 (34.6)	17 (65.4)	
Definitive treatment, no. (%)			0.417
Monotherapy	4 (66.7)	2 (33.3)	
Combination therapy	20 (46.5)	23 (53.5)	
Inappropriate empirical therapy	37 (51.4)	35 (48.6)	0.172
Appropriate definitive therapy	24 (49.0)	25 (51.0)	0.840
INCREMENT-CPE mortality score			<0.001
0–7	25 (54.3)	4 (7.7)	
8–15	21 (45.7)	48 (92.3)	

11.0% in 2014, respectively [10]. Although CRE infections have been reported many times regarding the risk factors and effect on mortality [3–5]. However, limited information is available about the treatment options that physicians used to fight CRE infections in China. In the present study, a retrospective analysis was conducted to analyze the treatment options and clinical outcomes in a five-year hospital-based study of 98 patients with bloodstream infection (BSI) caused by CRE in a Chinese university hospital (Fuzhou, China).

Materials and methods

Study setting

This study was conducted between January 2011 and December 2015 in Fujian Medical University Union Hospital, which is a 2200-bed tertiary-care teaching hospital with approximately 95,000 hospital admissions per year.

Study design

This was a retrospective observational study that included consecutive inpatients with BSI CRE infections. CRE BSI is a serious infection defined by the presence of CRE in the bloodstream as evidenced by positive blood cultures in cases where contamination has been excluded. During the same admission episode (from admission until hospital discharge), if a patient had more than one times positive blood culture of same species with identical susceptibility pattern, repeat isolates were excluded. Only the first BSI-episode was included in the analysis [11,12]. Hospital-onset bloodstream infection: bloodstream infection that is first identified (culture drawn) ≧48 h after hospital admission. Community-onset bloodstream infection: bloodstream infection occurring in an outpatient or first identified (culture drawn) <48 h following admission to hospital [11,12]. Enrolled patients were followed up twice a week until discharge or death. The study was approved by the institutional review board of Fujian Medical University Union Hospital.

Microbiology

Species identification and susceptibility testing were performed in the clinical laboratory by Vitek-2 Compact system (bioMérieux, France). Carbapenem (imipenem, meropenem and/or ertapenem) resistance was confirmed by disk diffusion method.

Following the criteria of the CLSI [13], CRE were defined as *Enterobacteriaceae* showing decreased susceptibility to

carbapenems (diameter for imipenem ≤ 19 mm, meropenem ≤ 19 mm, or ertapenem ≤ 18 mm) in this study.

Data collection and definitions

We reviewed the medical records and collected the case information. A standard surveillance form was used to collect the epidemologic and clinical data, including demographics (sex and age), prior hospitalization, treatment of the bacteremia episode, and outcome. Onset of BSI was defined as the date of collection of first blood culture that produced the CRE. BSI were classified according to standard criteria [14]. Neutropenia was defined as a neutrophil count lower than 1000/mm^3. Severity of BSI was classified as sepsis, severe sepsis and septic shock [15]. Treatment given before obtaining susceptibility results was defined as empirical. Antimicrobial treatment given after the susceptibility results was defined as definitive. Treatment regiments were classified as monotherapy (treatment with one in vitro active agent) and combination therapy (treatment with two or more in vitro active agents).

Statistical analysis

Data were processed and analyzed using the SPSS 19.0. The outcome measured was the all-cause mortality within 30 days after the onset of bacteremia. Patients discharged before day 30 or hospitalized and alive at day 30 were considered survivors. Survivors and non survivors were compared to identify factors associated with mortality. Categorical variables were assessed using χ^2 test or two-tailed Fisher exact test and were presented as percentages. The days from the first positive blood culture to death in the hospital within 30 days was displayed in a Kaplan–Meier curve. A log rank test was used to compare different groups. A Cox proportional hazards model was used to identify factors independently associated with mortality. We investigated the INCREMENT-CPE mortality score (0–7 [low mortality score] versus 8–15 [high mortality score]) to predict all-cause mortality in patients with BSIs due to CPE according to previous study [16]. All tests were two-tailed, with the significance level set at 0.05.

Results

Patients and distribution of isolates

Blood cultures were positive in 5724 cases (5.5%) during the study period in our hospital. 98 patients diagnosed with CRE BSI were identified during the study period. 68 (69.4%) were male, and 30 (30.6%) were female (Table 1). The mean patient age was 47.3 years (standard deviation [SD], 24.5 years) (median, 48.5 years; range, 5 months to 93 years). All episodes of CRE BSI were hospital acquired. The median duration for hospitalization before the onset of bacteremia was 15 days (interquartile range 0–84 days). The most common organism isolated was *Klebsiella pneumoniae* (78 cases, 79.6%), followed by *Enterobacter cloacae* (12 cases, 12.2%), *Klebsiella oxytoca* (4 cases, 4.1%), *Escherichia coli* (3 cases, 3.1%) and *Citrobacter freundii* (1 cases, 1.0%). The distribution and MICs of carbepenem resistant *Enterobacteriaceae* isolates in our study were shown in Table 2.

Treatment

For empirical treatment, 26 patients (26.5%) received at least one active drug within 48 h after the onset of bacteremia, while 72 patients (73.5%) received no active drug during the first 48 h of the infection. Among patients who were received empirical monotherapy, 21 patients had good therapeutic effect. The antibiotic regimens used in these patients had not been changed although the susceptibility results available showed the antibiotics were all resistant (Fig. 1).

Table 2
Distribution and MICs of Carbepenem resistant *Enterobacteriaceae* isolates in this study.

Microorgainisms	Number	IPM MICs (μg/ml, Vitek-2)			ETP MICs (μg/ml, Vitek-2)		
		≥16	8	4	≥8	4	2
Klebsiella pneumoniae	78	71	4	3	76	2	–
Klebsiella oxytoca	4	3	–	1	3	1	
Enterobacter cloacae	12	2	7	3	7	4	1
Escherichia coli	3	–	2	1	2	1	–
Citrobacter freundii	1	1	–	–	1	–	–
Total	98	77	13	8	89	8	1

Table 3
Outcome of patients with CRE bloodstream infections accroding to treatment regimen.

Antimicrobial regimen	No. of patients			Mortality, %
	Total	Survived	Died	
Combination therapy	43	20	23	53.5
Carbapenem-containing regimen		6	7	53.8
+amikacin		2		
+tigecycline		3	5	
+tigecycline + quinolone			2	
+tigecycline + amikacin		1		
Carbapenem-sparing regimen		14	16	53.3
Tigecycline + amikacin		1	4	
Tigecycline +quinolone		2	4	
Amikacin + quinolone		2		
Tigecycline + colistin			1	
Other				
Amikacin +other		4	2	
Quinolone + other		3	1	
Tigecycline + other		2	4	
Tigecycline-containing regimen		9	20	69.0
Tigecycline-sparing regimen		11	3	21.4
Monotherapy	6	4	2	33.3
Colistin	3	1	2	
Cefepime	1	1		
Moxifloxacin	1	1		
Latamoxef	1	1		
No active agent	33[a]	22	11	33.3

[a] Six patients were infected with panresistant *Enterobacteriaceae*.

For definitive treatment, 49 patients (59.8%) received at least one active drug and 33 patients (40.2%) received therapy with no active drug, including 21 patients with monotherapy and 12 patients with combination therapy (Table 3). 8 patients were infected with panresistant CRE (Fig. 1).

Outcome

The all-cause 30-day mortality was 53.1% (52 of 98 patients died). The mortality was almost the same (53.8% versus 53.3%) among the patients treated with carbapenem-containing regimen and those with carbapenem-sparing regimen (Table 2). 30-day mortality was significantly higher in the patients treated with tigecycline-containing regimen than in those who received therapy

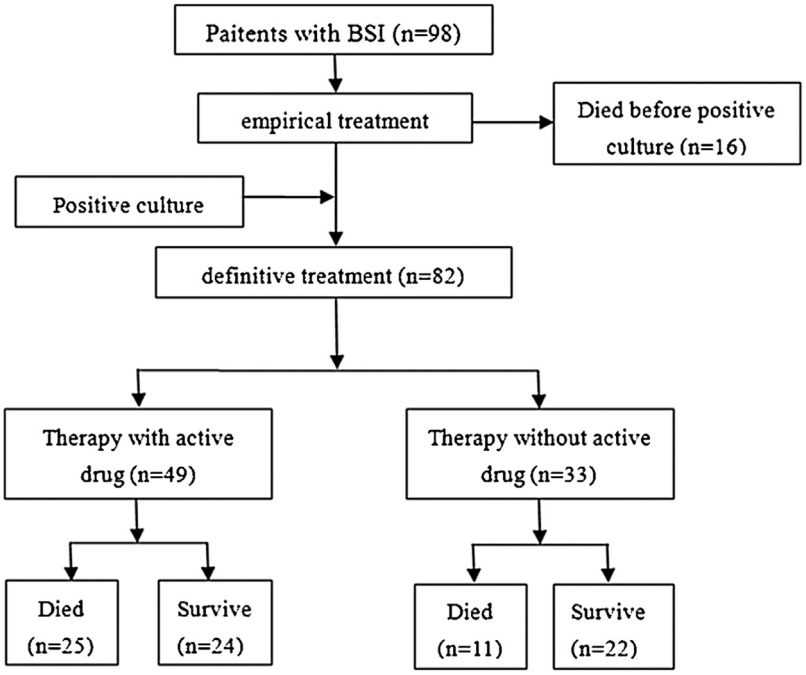

Fig. 1. Study selection flow chart. BSI, bloodstream infection.

with tigecycline-sparing regimen (69.0% versus 21.4%) (Table 3). Totally, 49 patients received no active agent therapy. Among these patients, 16 patients died within 48 h after the onset of CRE BSI, before the susceptibility results were available. 66.7% (22/33) patients who received no active drugs survived after the susceptibility results available.

The effects of host-, infection-, and treatment-related factors on 30-day mortality were analyzed in a univariate analysis (Table 1). We dichotomised the INCREMENT-CPE mortality score into 0–7 (low mortality score) and 8–15 (high mortality score) points. 30 day mortality in the low-mortality-score group was shown by 45.7% compared with 92.3% in the high-mortality-score group. Adverse outcome appeared to be more likely among patients with previous carbapenem exposure, neutropenia, severity of septic, and time to initiation of BSI. There was no significant difference in the mortality among the patients who received monotherapy and who received combination schemes (33.3% versus 53.5%; $p = 0.105$). The Kaplan–Meier survival estimates over time also showed no significantly better for either of patients treated with monotherapy and combination schemes ($p = 0.381$) (Fig. 2). Within the different treatment groups, the lowest mortality rate (33.3%) was observed in patients treated with monotherapy (Table 3).

By entering the host-, infection-, and treatment-related variables with potential effect on mortality in the Cox proportional hazards model, severity of sepsis (hazards ratio [HR], 1.307; 95% confidence interval [CI], 1.005–1.070; $p = 0.021$), INCREMENT-CPE mortality score (hazards ratio [HR], 26.774; 95% confidence interval [CI], 2.736–261.998; p = 0.005) and neutropenia (HR, 73.187; 95% CI, 6.439–831.866; $p = 0.001$) were identified as independent predictors of mortality (Table 4).

Discussion

Over the past decade, CRE have been considered as a cause of difficult-to-treat infections associated with worse outcome in the healthcare settings [2]. The increasing prevalence and high mortality with CRE highlight the importance of effective therapy for those infections caused by the organisms. In this study, we focused on the treatment regimen and clinical outcomes of CRE bloodstream infection in one university hospital in China.

Our study involved 98 patients with bacteria due to CRE. The overall mortality rate was 53.1%, which is similar with that in previous studies [17,18]. The result probably reflects that greater awareness and action should be placed on the multidrug resistance bacteria. Notably, a surprisingly high percentage of inappropriate empirical treatment (73.5%) was observed in this study, which is much higher than others reported in previous similar studies [19–21]. The reasons are probably as follows: 1. most doctors probably lack general overview of the prevalence of CRE infections and CRE bacteremia in our hospital. So CRE bacteremia was not obtained enough concerned during diagnosis. 2. Most doctors in our hospital tended to be deficient in recognizing patients who were at high risk of CRE bacteremia. Therefore, the antibiotics used during empitical therapy could not cover those multidrug-resistant organisms.

Treatment regimens for CRE infections varied widely nowadays [19,22]. Mono and combination therapy could be used to combat CRE infections. Carbapenem-containing combination therapy may be more beneficial than carbapenem-sparing combination therapy in the treatment of CRE BSIs. However, no significant differences were found between the two groups in our study.

Many researchers suggested that combination therapy should be used during treatment so that a better outcome may be obtained in patients with CRE infection than those with monotherapy [6–9]. Also, a consensus for the treatment of CRE infection [23] recommended combination therapy to treat critically ill patients in China. Therefore, combination therapy tended to be used to cover extremely resistance bacteria in China nowadays, which can been found that the majority of patients (87.8%, 43/49) in our study received combination therapy for definitive treatment (Table 3). Mortality was almost same between patients who received carbapenem-containing combination treatment and those who got combination without carbapenems, which was different with previous studies [18]. “Carbapenem effect” probably was the reasonable explanation for our observation because it was unlikely to occur against CRE with high MICs of carbapenem [18]. Because the number of patients who received monotherapy was too

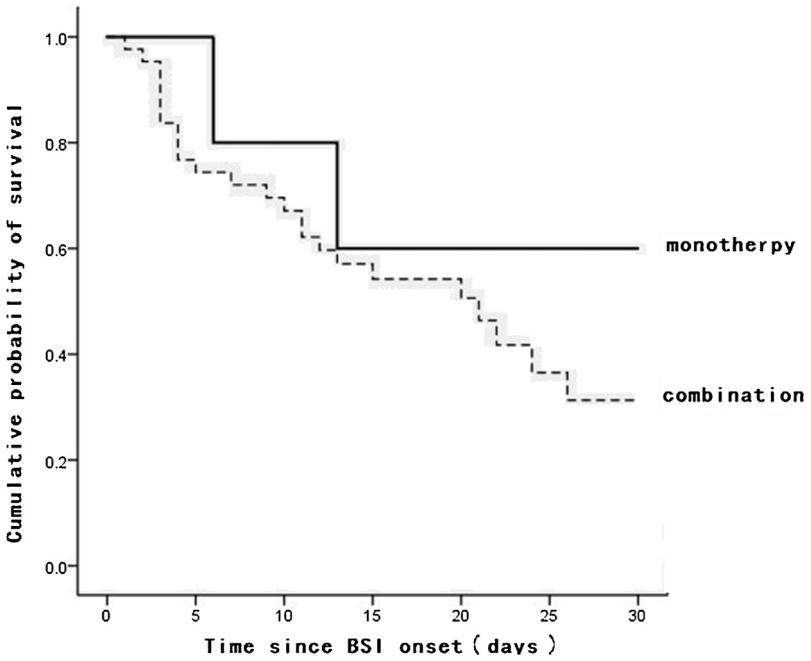

Fig. 2. Kaplan–Meier survival estimates of patients with CRE-BSIs according to treatment regimen: combination therapy (dotted line) versus monotherapy (continuous line). p = 0.381 (log rank test).

Table 4
Cox proportional hazards model of factors associated with all-cause 30-day mortality in 98 patients with CRE bloodstream infections.

Variables	Crude Cox		Adjusted Cox	
	HR (95% CI)	P	HR (95% CI)	P
Age (per 1-year increase)	0.999 (0.981–1.017)	0.915	0.851 (0.387–1.870)	0.687
Gender (female and male)	1.042 (0.46–2.362)	0.921	0.878 (0.33–2.991)	0.794
Polymicrobial BSI	1.846 (0.821–4.153)	0.138	1.089 (0.396–4.286)	0.869
Neutropenia (yes/no)	2.491 (1.089–5.698)	0.031	73.187 (6.439–831.866)	0.001
Severity of sepsis	3.95 (1.355–11.516)	0.012	1.037 (1.005–1.070)	0.021
ICU stay	0.681 (0.306–1.519)	0.348	8.725 (0.897–84.9)	0.062
Monotherapy/combination therepy	0.564 (0.133–2.399)	0.439	1.012 (0.15–6.842)	0.990
Previous carbapenem exposures	0.662 (0.248–1.756)	0.409	2.386 (0.665–8.562)	0.182
INCREMENT-CPE mortality score	15.864 (2.15–117.29)	0.007	26.774 (2.736–261.998)	0.005

small for definitive treatment, the therapeutic effect could not be assessed accurately between the two groups of patients with combination therapy versus monotherapy. Additionally, it should be noted that most of patients (66.7%) survived who were treated with no active agent even when the susceptibility results were available in this study. The plausible explanation is that these episodes were transitory bacteremia and not truly bacteremia.

Interestingly, a significantly higher mortality rate was observed in patients treated with tigecycline-containing regimen than in those treated with tigecycline-sparing regimen in this study. The result maybe due to the following reason. The patients in death group had more neutropenia than those in survival group ($p = 0.005$, Table 1). In our study, most of patients (70.0%, 20/29) treated with tigecycline-containing regimen came from the death group and it probably led to the excess deaths in patients for whom tigecycline was included in the combination therapy.

Indeed, our results demonstrated several factors probably associated with adverse outcome. Among these factors, neutropenia, severity of sepsis have been described in other studies [4,19]. One intriguing observation in the univariate analysis was that previous carbapenems exposure was highly associated with mortality. The factor was previously considered to be risk factor for CRE infection [17,24–26]. Given the results of this and previous studies, patients with CRE BSI should be paid particular attention during treatment, and more effective approaches for treatment of these patients should be considered and adopted to reduce the mortality. Our data suggested that empirical treatment should be able to cover CRE in patients previous exposed to carbapenems.

Furthermore, we identified three independent clinical risk factors (INCREMENT-CPE mortality score, severity of sepsis and neutropenia) for mortality. As a new score system, INCREMENT-CPE mortality score was proved to be valuable in predicting mortality. It could help identify patients at high risk for early mortality, which may be useful for making decisions on the management of patients with BSIs due to CPE [16]. Severity of sepsis was found to be one risk factor for mortality in previous study [18]. Sepsis is an important and common problem among critically ill patient worldwide, with a strong relationship with length of hospital stay and mortality [26,27]. In some cases, sepsis may not be obvious. Therefore, it should be often required to make right medical diagnosis to save patient's life. Neutropenic patients lack the ability to combat bacterial infections, and they rely on immediate treatment with antibiotics that kill infecting bacteria. Thus, there might be a need for new therapeutic management in patients with neutropenia.

The present study has some limitations. First, this is a single-center study with a relatively small sample size. Therefore, the power of treatment regimen and the outcome studies was limited, and our outcome probably did not apply to other institutes

in different regions in China. Second, the carbapenem MIC values of CRE isolates in this study were not available, which limited our ability to evaluate the influence of different carbapenem MICs on clinical outcome. Third, We did not detect the carbapenem resistance mechanisms of our CRE isolates and suboptimal confirmatory testing (disc diffusion rather than e-test or agar/broth dilution).

In conclusion, our study demonstrated a high mortality associated with CRE BSI and a high percentage of inappropriate empirical treatment for CRE BSI patients in a Chinese teaching hospital. Particular attention should be given to the patients with CRE BSI.

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Competing interests

None declared.

Ethics approval

This study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki. In this observational research, no additional medical procedure was performed and all data were retrieved from the medical records of the treated patients. All information was, however, given to the patients and, in accordance with the Chinese legislation, patients could refuse the use of their medical data.

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