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ORIGINAL RESEARCH

Ceftazidime-Avibactam for Carbapenem-Resistant Gram-Negative Bacteria Infections: A Real-World Experience in the ICU

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Purpose: Ceftazidime-avibactam (C-A) is a treatment option for carbapenem-resistant gram-negative bacterial (CR-GNB) infections, but little is known regarding its suitability for the intensive care unit (ICU). The current study aimed to analyze use of C-A for critically ill patients, determine independent predictors of clinical outcome and mortality and explore routine dosages for patients in continuous renal replacement therapy (CRRT).

Patients and Methods: A single-center, retrospective and observational study was conducted in critically ill patients receiving different C-A-based therapies for CR-GNB infections in a tertiary teaching hospital in Beijing, China. Demographic data, severity of infection, clinical outcomes and mortality were assessed. The primary and secondary outcome of this study was 90-day all-cause mortality and 14-day clinical response, respectively.

Results: A total of 43 patients with CR-GNB infection were enrolled, including 14 (32.6%) patients received C-A monotherapy. C-A monotherapy and combination with other agents did not affect 14-day clinical response or 90-day survival. All-cause mortality at 90-days was 39.5% (17/43). Multivariate Cox analysis showed that concomitant with bloodstream infection was independent risk factors for 90-day mortality and that the time to initiation of C-A and Acute Physiology and Chronic Health Evaluation (APACHE) score was independent predictors of 14-day clinical response. Five CRRT patients who received high-dose C-A therapy (>3.75 g/d) had prolonged survival compared with 5 who received low-dose C-A (<3.75 g/d, $p = 0.03$).

Conclusion: C-A was an effective therapy for severe CR-GNB infections and clinical response correlated with the time of C-A initiation. A dosage >3.75g/d C-A was associated with prolonged survival of CRRT patients. Randomized controlled trials or multicenter studies are needed to confirm these findings.

Keywords: ceftazidime-avibactam, renal replacement therapy, infections, intensive care unit, carbapenem-resistant gram-negative bacteria

Introduction

There has been a recent rise in the detection of carbapenem resistant gram-negative bacteria (CR-GNB), especially during infections caused by Acinetobacter baumannii, Enterobacter spp., dominated by Klebsiella pneumoniae, and Pseudomonas aeruginosa.[1,2] CR-GNB infections have limited treatment options and antimicrobial drugs, such as polymyxins and aminoglycosides, are the last line of treatment.[3] Such drugs may cause adverse reactions, such as nephrotoxicity,[4] and CR-GNB resistance shows an ascending trend.[5] Accordingly, there is an urgent need for new antimicrobial drugs.[6]

Nosocomial CR-GNB infection dramatically increases mortality, morbidity, length of stay and hospitalization expenses of intensive care unit (ICU) patients. ICU patients are more likely to need CRRT treatment, a risk factor for mortality.[7,8] Ceftazidime-

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avibactam (C-A) is a novel β-lactam/β-lactamase inhibitor combination which was approved by the US Food and Drug Administration (FDA) in 2015[9] and received marketing approval in China in September 2019 for treatment of CR-GNB infections. Adverse reactions caused by C-A, including nephrotoxicity, are milder than for polymyxins and aminoglycosides,[10] making C-A highly promising.[11] Optimal C-A dosages for CRRT patients remain to be identified and controversies have arisen over whether C-A should be given alone or in combination.[12]

Limited data exist regarding use of C-A for ICU patients. The current study analyzed data from ICU patients in a tertiary first-class hospital in Beijing to explore real-world experience and determine a reference for C-A utilization.

Materials and Methods

Patients and Study Setting

A single-center, retrospective, observational cohort study was conducted at Peking Union Medical College Hospital, a 2000-bed tertiary teaching hospital in Beijing, between August 31, 2019, and December 31, 2022. Inclusion criteria were as follows: (1) age ≥18 years and treated with C-A ≥48 hours; (2) confirmation of CR-GNB infection by drug susceptibility testing before C-A treatment; (3) critically ill patients in the ICU. Exclusion criteria were as follows: (1) <48 hours history of C-A treatment; (2) C-A treatment within 3 months prior to hospital admission; (3) incomplete medical records during C-A treatment. In cases of multiple C-A prescriptions for CR-GNB infection, only the first episode (>48 h) was considered. The patients in the study were enrolled with the assistance of an infectious disease physician. C-A dosages were adjusted based on renal function according to the package insert of C-A.[13] All enrolled patients were followed up for 90 day to record survival status.

Data Collection

All patients receiving C-A were recorded in the ward pharmacy system of Peking Union Medical College Hospital and were filtered according to inclusion and exclusion criteria. Demographic, length of hospitalization (including length of ICU stay), clinical (diagnosis, pathogenic bacteria, clinical response) and other data were extracted from the electronic record of the Hospital Information System (HIS). Comorbidities, previous hospitalization, surgery and antibiotic use during 90 days prior to admission were obtained from admission records. Disease severity was evaluated by APACHE II score and the highest score within 24 hours of treatment recorded. Some patients were discharged from hospital before 90 days and followed up with the assistance of the department of medical records to record survival status.

Definitions and Patient Outcomes

Definitions

Fourteen-day favorable clinical response comprised clinical cure, defined as improvement in clinical signs and symptoms and termination of antibacterial therapy, and clinical improvement, defined as partial improvement in signs and symptoms but with continued or de-escalated antibacterial therapy. Fourteen-day unfavorable clinical response comprised persistence of signs and symptoms, death or infection recurrence.[14,15]

Time to initiation of C-A was measured in days between time of index culture and receipt of the first C-A dose.[16,17] CRRT patients were defined as receiving treatment of CRRT during C-A therapies. Dose was defined as the most frequent dose or the last used during CRRT treatment. Combination C-A therapy was defined as receiving a secondary agent for more than 48 hours.

Patient Outcomes

The primary outcome was 90-day all-cause mortality. The secondary outcome was 14-day clinical response. Optimal C-A dose to produce improved survival of CRRT patients for clinical outcomes of critically ill patients were also determined.

Microbiology

Identification of micro-organisms was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS). All strains were tested for susceptibility to β-lactam, aminoglycoside and quinolone antibiotics. Minimum inhibitory concentrations (MICs) were based on Clinical and Laboratory Standards Institute (CLSI) guidelines. Carbapenem resistance was defined as resistance to ertapenem at a MIC > 2 mg/mL and resistance to imipenem or meropenem at a MIC > 4 mg/mL.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software. Normally distributed data are expressed as mean ± SD and were analyzed by independent sample *t*-test. Non-normally distributed data are expressed as median values (quartiles) and were analyzed by Mann–Whitney *U*-test. Categorical variables are expressed as n (%). Differences were compared using chi-square test or two-tailed Fisher's exact test. Multivariate regression analysis was performed in a reverse stepwise manner to identify risk factors for unfavorable clinical response. Non-parametric tests were used to compare differences between groups of non-normally distributed data. Fisher's Exact Test was used to compare rates between groups. A two-sided p value <0.05 was considered to indicate statistical significance. The Kaplan–Meier method was used for survival analysis.

Results

Baseline Data of 43 Patients

A total of 101 patients were evaluated and 43 ICU patients were enrolled (Figure 1). Patients were divided into two groups (90-survival or 90-died group) based on primary outcome of 90-day all-cause mortality and demographic, clinical and infection data are shown in Table 1. Twenty-six patients survived at 90 days and 17 died. C-A monotherapy and combination had no significant effect on 90-day mortality ($p = 0.307$). More surviving patients suffered from pulmonary infections than those who had died ($p = 0.014$) and less in bloodstream infection ($p = 0.036$). ECMO use ($p = 0.039$) and C-A dose ($p = 0.004$) differed between the two groups (90-day survival group and died group).

Independent Predictors of 90-Day All-Cause Mortality

All-cause mortality rates were 39.5% (17/43) at 90-days. Cox regression analysis was conducted for variables with p-value <0.1 and results are presented in Table 2. Presence of bloodstream infections ($p = 0.033$) was an independent risk factor for 90-day mortality. Patients receiving higher doses of C-A treatment had lower 90-day mortality ($p = 0.027$).

Risk Factors for Unfavorable 14-Day Clinical Response in CR-GNB-Infected Patients

The 14-day favorable clinical response rate was 55.8% (24/43) and demographic and clinical characteristics of patients divided by clinical response are shown in Table S1. Logistic regression analysis was performed for all factors with a p-value <0.1. APACHE II score and increased time to initiation of C-A therapy were risk factors for C-A treatment failure (Table 3). The median time to initiation of C-A in favorable clinical group was 4.5 days.

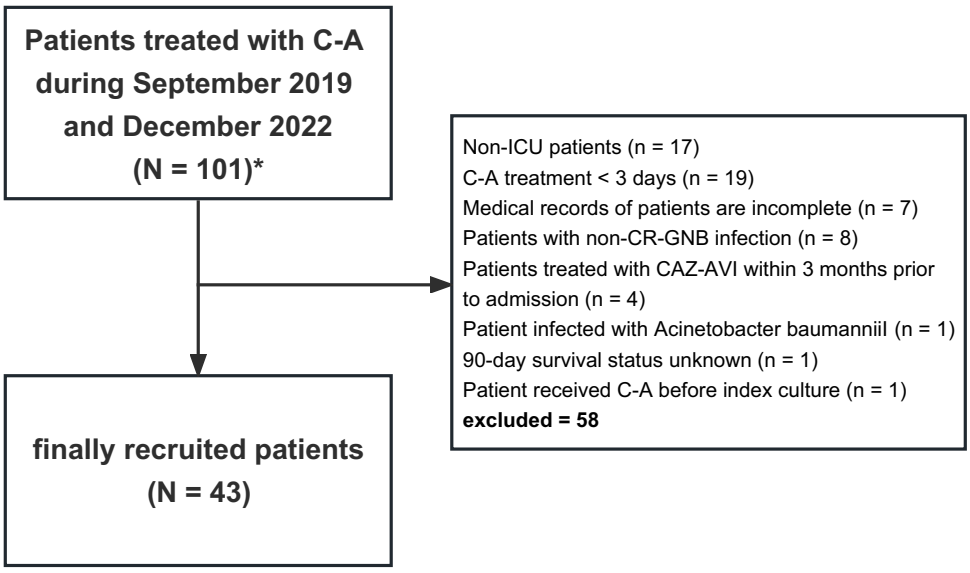

Figure 1 Flowchart of patient selection. *Only the first episode of C-A therapies was included. The same cases have been rectified in 101 patients.

Table 1 Baseline Characteristics of 43 Patients Survived and Died on 90 Days

	Total (n = 43)	Survived (n = 26)	Died (n = 17)	*P*-value
Demographic characteristics				
Gender				
Male (n, %)	28 (65.1%)	17 (65.4%)	11 (64.7%)	0.964
Age (mean ± S.D.)	57.98± 16.19	55.23± 17.22	62.18± 13.92	0.172
Age > 60 years (n, %)	21 (48.8%)	12 (46.2%)	9 (52.9%)	0.663
BMI[a]	22.86 (21.51–27.04)	24.22 (21.45–27.42)	22.86 (21.54–24.85)	0.332
Obese (n, %)[b]	6 (14.0%)	4 (15.4%)	2 (11.8%)	1.000
Underlying diseases (n, %)				
Hypertension	22 (51.2%)	11 (42.3%)	11 (64.7%)	0.151
Other cardiovascular disease	30 (69.8%)	17 (65.4%)	13 (76.5%)	0.439
Diabetes mellitus	14 (32.6%)	9 (34.6%)	5 (29.4%)	0.722
Chronic liver disease	15 (34.9%)	9 (34.6%)	6 (35.3%)	0.964
Chronic respiratory disease	9 (20.9%)	7 (26.9%)	2 (11.8%)	0.417
Chronic kidney disease	15 (34.9%)	9 (34.6%)	6 (35.3%)	0.964
Malignancy	12 (27.9%)	7 (26.9%)	5 (29.4%)	1.000
Solid organ transplantation	4 (9.3%)	3 (11.5%)	1 (5.9%)	0.930
Immunosuppressive disease	10 (23.3%)	4 (15.4%)	6 (35.3%)	0.254
Infection site variables				
Pulmonary infection	38 (88.4%)	26 (100.0%)	12 (70.6%)	0.014*
Bloodstream infection	17 (39.5%)	7 (26.9%)	10 (58.8%)	0.036*
Intra-abdominal infection	10 (23.3%)	4 (15.4%)	6 (35.3%)	0.254
Urinary tract infections	8 (18.6%)	3 (11.5%)	5 (29.4%)	0.284
Microbiology characteristic (n, %)				
CR-GNB variables				
Klebsiella pneumoniae	15 (34.9%)	8 (30.8%)	7 (41.2%)	0.484
Pseudomonas aeruginosa	2 (4.7%)	2 (7.7%)	0 (0.0%)	0.511
Enterobacter cloacae	2 (4.7%)	1 (3.8%)	1 (5.9%)	1.000
Multiple CR-GNB infection	24 (55.8%)	15 (57.7%)	9 (52.9%)	0.759
Concomitant with GPB infection	16 (37.2%)	11 (42.3%)	5 (29.4%)	0.392
Severity variables				
Length of hospitalization (days)[a]	42.0 (22.0–69.0)	38.0 (21.0–73.8)	42.0 (22.0–64.5)	0.960
ICU duration (days)[a]	24.0 (17.0–44.0)	22.5 (14.5–45.0)	33.0 (17.5–44.5)	0.441
Sepsis (n, %)	11 (25.6%)	5 (19.2%)	6 (35.3%)	0.411
Septic shock (n, %)	26 (60.5%)	14 (53.8%)	12 (70.6%)	0.272
APACHE II (mean ± S.D.)	21.53 ± 3.33	21.04 ± 3.10	22.29 ± 3.60	0.230
Therapeutic interventions				
CRRT (n, %)	17 (39.5%)	8 (30.8%)	9 (52.9%)	0.146
Duration of ventilator (hours)[a]	250.0 (80.0–928.0)	151.5 (45.5–758.5)	514.0 (172.0–980.0)	0.053
ECMO (n, %)	4 (9.3%)	0 (0.0%)	4 (23.5%)	0.039*
Treatment-related characteristic				
CrCL (n, %)[c]				
< 50	18 (41.9%)	9 (34.6%)	9 (52.9%)	0.234
50 < CrCL < 130	13 (30.2%)	8 (30.8%)	5 (29.4%)	0.925
≥ 130	12 (27.9%)	9 (34.6%)	3 (17.6%)	0.387
Dosage of C-A (g / day)[a]	5.00 (3.75–7.50)	7.50 (4.69–7.50)	3.75 (2.50–6.25)	0.004*
The time to initiation of C-A (days)[a]	5.0 (3.0–10.0)	4.5 (2.8–7.3)	5.0 (3.0–17.0)	0.147
C-A monotherapy treatment (n, %)	14 (32.6%)	10 (38.5%)	4 (23.5%)	0.307

Notes: [a]Data are presented as median (interquartile range [IQR]). [b]Obese was defined as patients BMI ≥ 28 kg/m^2. [c]Creatinine clearance (mL/min) was calculated by using the Cockcroft-Gault formula. *$P < 0.05$, there was statistically significant difference.

Abbreviations: BMI, Body mass index; GPB, Gram-positive bacteria; C-A, Ceftazidime-avibactam; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, Continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; CrCL, creatinine clearance; IQR, Interquartile range.

Table 2 Univariate and Multivariate Cox Proportional Hazards Model Analysis Associated with 90-Day Mortality

	P value	HR (95% CI)	P value	HR (95% CI)
Dosage of C-A	0.003*	0.706 (0.561–0.889)	0.027*	0.723 (0.543–0.963)
Pulmonary infection	0.016*	0.272 (0.095–0.781)	0.638	0.756 (0.235–2.427)
Bloodstream infection	0.045*	2.694 (1.021–7.105)	0.033*	3.164 (1.095–9.137)
Duration of ventilator	0.943	1.000 (1.000–1.000)	0.658	1.000 (1.000–1.001)
ECMO	0.005*	4.982 (1.605–15.462)	0.160	2.561 (0.689–9.516)

Note: *$P < 0.05$, there was statistically significant difference.
Abbreviations: HR, Hazard ratios; CI, Confidence interval; C-A, Ceftazidime/avibactam; ECMO, Extracorporeal Membrane Oxygenation.

Table 3 Multivariate Logistic Regression Analysis of Variables Associated with Unfavorable Clinical Response

	Univariate Analysis		Multivariate Analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Bloodstream infection	0.122	2.698 (0.766–9.506)	0.157	3.180 (0.640–15.789)
ICU duration (days)	0.834	0.999 (0.989–1.009)	–	–
APACHE II	0.019*	1.301 (1.044–1.620)	0.007*	1.485 (1.113–1.980)
CRRT	0.224	2.186 (0.620–7.700)	–	–
Duration of ventilator (hours)	0.880	1.000 (1.000–1.001)	0.596	1.000 (1.000–1.001)
ECMO	0.999	–	–	–
The time to initiation of C-A (days)	0.081	1.118 (0.986–1.267)	0.049*	1.174 (1.001–1.377)

Note: *$P < 0.05$, there was statistically significant difference.
Abbreviations: OR, odds ratios; CI, Confidence interval; C-A, Ceftazidime-avibactam; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, Continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

C-A Dosage of CRRT Patients

A total of 17 patients were treated with CRRT and were divided into 3 groups by daily C-A dosage. Baseline variables were not significantly different between the three groups (daily dose >, = or < 3.75g/day group) (Table 4). Kaplan–Meier survival analysis was performed, using dosage as a variable (Figure 2). Patients with C-A dosing >3.75 g/day were associated with a higher survival rate than C-A dosing <3.75 g/day, $p = 0.03$.

Table 4 Baseline Characteristics of 17 Patients Treated with CRRT

	> 3.75g/d (n = 5)	= 3.75 (n = 7)	< 3.75 (n = 5)	*P*-value
Demographic characteristics				
Gender				
Male (n, %)	3 (75.0%)	3 (42.9%)	3 (60.0%)	0.816
Age > 60 years	1 (25.0%)	3 (42.9%)	2 (40.0%)	1.000
Single site of infection	1 (25.0%)	3 (42.9%)	0 (0.0%)	0.288
Single CR-GNB infection	0 (0.0%)	4 (57.1%)	1 (20.0%)	0.167
Concomitant with GPB infection	1 (25.0%)	2 (28.6%)	2 (40.0%)	1.000
Concomitant with fungal infection	2 (50.0%)	4 (57.1%)	2 (40.0%)	1.000
Concomitant with virus infection	0 (0.0%)	2 (28.6%)	1 (20.0%)	0.750
Therapy of C-A single (n, %)	1 (25.0%)	3 (42.9%)	2 (40.0%)	1.000
APACHE II	26.0 (19.0–27.0)	22.0 (21.0–24.0)	26.0 (18.0–28.0)	0.423
Sepsis	1 (25.0%)	2 (28.6%)	1 (20.0%)	1.000
Septic shock	2 (50.0%)	4 (57.1%)	4 (80.0%)	0.668

Abbreviations: GPB, Gram-positive bacteria; C-A, Ceftazidime-avibactam; APACHE, Acute Physiology and Chronic Health Evaluation.

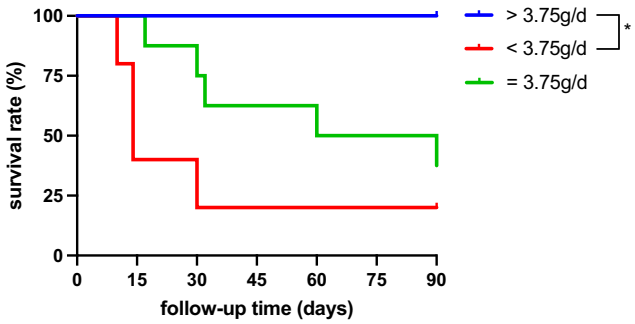

Figure 2 Survival curves of dosage of 17 patients treated with CRRT. Single trial with n = 5 (> 3.75 g/d), n = 7 (= 3.75 g/d) and n = 5 (< 3.75 g/d); Log rank test was used to evaluate the difference. *P = 0.03.

Discussion

C-A is the last line of therapy for severe CR-GNB infections, but little data exist to characterize the response of critically ill patients or to indicate appropriate C-A dosages during CRRT. The current cohort included 43 ICU patients with CR-GNB infections. All-cause mortality, clinical responses to C-A treatment were used to evaluate clinical efficacy.

The 90-day all-cause mortality was 39.5% (17/43). Shields et al have reported a mortality of 31% for partial ICU patients with CRE infection, which is similar to our result. This suggests that C-A is a promising option for patients with severe infections. Cox analysis showed that bloodstream infection increased the risk of 90-day mortality. Additionally, a multicenter retrospective study by Balandín et al in ICU patients with GNB infections showed bacteremia, and the need for life-support were independent predictors of mortality by multivariate analysis.[18] Meanwhile, the Cox model in our study also indicated that receiving higher doses of C-A had lower 90-day mortality.

We had a 14-day clinical response 55.8% compared with 59.6% from the study including 34% ICU patients with CR-KP infections of Wang et al.[14] The logistic model showed that the timing of C-A initiation was associated with a 14-day clinical response in patients. A single-center retrospective study by Zilberberg et al[19] showed a significant increase of in-hospital mortality in patients who received inappropriate initial antibiotic therapy. The CR-GNB infections in the patients in this study were all C-A sensitive, so the C-A-based regimen was appropriate. Our results may suggest, to some extent, that the earlier a patient receives appropriate antimicrobial therapy, the better the clinical outcome of the patient may be.[17,19]

Limited data are available for C-A dosing during CRRT. To our knowledge, there had been no large, prospective assessments of C-A dosing in patients receiving CRRT. There were only 3 cases reported so far. Among them, dose regimens were 1.25g Q 8 h (3.75 g/day),[20] 2.5g Q 12h (5 g/day)[21] and 2.5g Q 8 h (7.5 g/day).[22] Soukup et al reported a critically ill patient treated with 2.5 g Q 8 h and had a significantly clinical improvement.[22] In addition, Zhang et al found a significantly better clinical outcome in patients treated with 2.5 g Q 12.[21] The above findings are consistent with our study. In addition to this, our study was of higher quality due to the inclusion of 17 patients with CRRT, an increased number compared to previous studies. Besides, Bavaro et al found that the use of a loading dose followed by an extended or continuous infusion dosing regimen of β-lactams in patients with GNB bacterial bloodstream infections may be related to reduced mortality.[23] This provides a new option for C-A therapy in patients with severe infections.

Several limitations of our study should be mentioned. First, it was a single-center, observational and retrospective study. Second, the sample size in our study was only 43 cases. However, as a national intensive care research center hospital, different types of ICU patients were included in our cohort, which was highly representative. Very promisingly, the results of our study would guide the treatment of the above patients. Besides, the innovation of this study is to offer insight into the timing of C-A initiation. Also, this is the first study to focus on C-A dosing in CRRT patients, except for case reports.

Conclusion

Patients in high suspicion of CR-GNB infection with a shorter time to initiation of C-A therapy were more likely to have a favorable clinical response. A C-A dosage above 3.75g/d appeared to be associated with better survival of CRRT patients. Further large-scale, prospective studies or multicenter studies are required for critically ill patients.

Abbreviations

C-A, Ceftazidime-avibactam; CR-GNB, carbapenem-resistant gram-negative bacterial; ICU, intensive care unit; CRRT, continuous renal replacement therapy; ECMO, extra-corporeal membrane oxygenation; APACHE, Acute Physiology and Chronic Health Evaluation; PMs, polymyxins; AGs, aminoglycosides; FDA, Food and Drug Administration; MALDI-TOF/MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; MIC, minimum inhibitory concentrations; CLSI Clinical and Laboratory Standards Institute; IQR, Interquartile range; BMI, Body mass index; GPB, Gram-positive bacteria; CrCL, creatinine clearance; HR, Hazard ratios; OR, odds ratios; CI, Confidence interval.

Data Sharing Statement

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

Ethics Approval

The research was conducted in accordance with the Declaration of Helsinki. All organs were donated voluntarily with written informed consent, and this was conducted in accordance with the Declaration of Istanbul. The study got approved by the Research Ethics Committee of Peking Union Medical College Hospital (I-22PJ203). The requirement of informed consent from patients including the review of their medical records was waived by the Committee, the reasons consisted of (1) the patients may suffer almost no risk from this study, and the risk less than a minimum, (2) the study had no negative influence on rights and interests of the patients, (3) the personal details of patients were anonymous and had no commercial interests.

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Author Contributions

All authors contributed significantly to the work reported, whether in terms of conception, study design, execution, acquisition of data, analysis and interpretation, or all of these; participated in the drafting, revision or critical review of the article; provided final approval of the version to be published; agreed on the journal to which the article was to be submitted; and agreed to take responsibility for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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