Prompting With Checklist for Early Recognition and Treatment of Acute Illness On The Prevention of Acute Kidney Injury in Patients With Septic Shock

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Abstract

Background: Early identification of septic patients at high risk for acute kidney injury (AKI), followed by timely and appropriate interventions, is crucial for improving patients' outcomes. Checklist for Early Recognition and Treatment of Acute Illness (CERTAIN) is a tool for evaluating and treating acute illness promptly based on best practices. We hypothesized that the use of CERTAIN would prevent the occurrence of AKI after septic shock.

Methods: This was a before-and-after study. CERTAIN, included the care bundles recommended in the Sepsis 3.0 and Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, used in daily practice to manage patients with septic shock. The primary outcome was the incidence of AKI within 72 hours in patients with septic shock. Secondary outcomes were mortality and major adverse kidney events (MAKES) at 90 days after exposure to AKI.

Results: 124 patients had been treated with CERTAIN, and 112 patients were in the Pre-CERTAIN group. AKI reduced significantly in the Post-CERTAIN group compared to the Pre-CERTAIN group within 72h after enrollment (55.7% vs 68.8%, $P=0.045$). CERTAIN prolonged ventilator-free days and vasoactive agents free days at 28 days (22 vs 17, $P<0.001$; 23 vs 19, $P=0.044$; respectively). The mortality and MAKES at 90 days were reduced in the Post-CERTAIN group compared to the Pre-CERTAIN group (17.7% vs 29.5%, $P=0.045$; 41.9% vs 56.3%, $P=0.039$; respectively).

Conclusions: Implementation of CERTAIN reduced the AKI frequency, mortality at 90 days, and the rate of MAKES at 90 days in septic shock patients.

Trial registration: [NCT01973829](https://clinicaltrials.gov/ct2/show/study/NCT01973829). Date of registration: 1st November 2013.

Background

Acute kidney injury (AKI) is common in critically ill patients and is associated with progression to chronic kidney disease (CKD) and higher in-hospital mortality and cost of care¹. Sepsis is a major etiology of AKI in the intensive care unit (ICU). Sepsis-associated acute kidney injury (SA-AKI) contributes to extremely high mortality of critically ill patients.² While patients who survived SA-AKI had relatively high rates of recovery and survival 1 year after sepsis.^{3,4} The current core problems were delayed diagnosis, inadequate diagnostic methods, and insufficient numbers of medical professionals capable of providing optimal management have contributed to adverse outcomes.⁵

Critically ill patients have complex conditions, and the staff in ICU are faced with time constraints, large amounts of clinical data, and a heavy workload. Failure to treat patients within the optimal therapeutic window, misjudgment, and miscommunication can result in adverse events and even death of the patients.⁶ In the era of evidence-based medicine and management based on clinical practice guidelines, Checklists are validated tools that can be used to standardize care models. Their application reduces certain types of adverse events in surgical departments.⁷⁻⁹ However, delays in the updating of

information, the incomplete usage of checklists, and the use of checklists only for monitoring purposes have indicated that checklists have not led to clinical improvements.¹⁰ Building upon these experiences and advances in modern technology, a novel electronic tool, the Checklist for Early Recognition and Treatment of Acute Illness and Injury (CERTAIN), is being developed to support the evaluation and treatment of critically ill patients following optimized clinical practices.¹¹ Due to the strong performance, we used CERTAIN based on sepsis 3.0 and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines to screen sepsis patients and initial the sepsis and KDIGO care bundles.

KDIGO guidelines were developed to promote the detection and prevention of AKI, thereby improving patient outcomes.¹ KDIGO care bundles focusing on optimization of fluid management and haemodynamic monitoring, avoidance of nephrotoxins, adjustment of medication doses according to renal clearance, tight glucose control, administration of renal replacement therapy if necessary.¹² Despite these bundles were nonspecific, the application of the KDIGO bundles in patients with nephrotoxic AKI or cardiac surgery-associated AKI had been shown a reduction in the occurrence of AKI progression.^{13,14} Whether KDIGO care bundles will decrease the incidence of AKI in patients with sepsis is still unknown.

This study aimed to use CERTAIN to select septic shock patients, who were then treated based on the KDIGO care bundles. We hypothesized that the use of the implementation of CERTAIN would reduce the incidence and severity of SA-AKI.

Methods

Study design and participants

This was a single-center before-and-after study performed in a comprehensive ICU in a tertiary public hospital in Tianjin. This study was carried out from April 1st, 2016, to June 1st, 2017. The study protocol was approved by the Ethics Committee of the Hospital of Tianjin First Center Hospital (approval No 2015KZ019). All patients provided informed consent. This trial was a subgroup analysis of a clinical trial registered at ClinicalTrials.gov (NCT01973829).

Participants were recruited from the patients admitted to the ICU with septic shock. Those 18 years or older were eligible to participate in this study. Patients enrolled in the study had to meet the criteria for Sepsis 3.0 with persistent hypotension requiring vasopressors to maintain MAP $\geq$ 65mmHg and having a serum lactate level $>$ 2mmol/L despite adequate volume resuscitation¹⁵. The exclusion criteria were pre-existing AKI ($\geq$ stage 1), advanced chronic kidney disease (CKD stage 4 and stage 5), hospitalization duration less than 72 hours, previous renal replacement therapy (RRT), renal transplantation, pregnancy, non-infectious causes of AKI (obstructive diseases of the urinary system, medications of nephrotoxic drugs and contrast-induced nephropathy), and participation in another interventional trial within the last 3 months.

Protocol Description

The protocol had 4 distinct phases. The first phase was the Pre CERTAIN stage. Patients with sepsis were treated before the usage of CERTAIN (April 1st, 2016 to August 31st, 2016). The treatment of the patients was made by their attending physician. The second phase, which we called the training phase, involved 1 month of training for the entire clinical team. The training was the implementation of CERTAIN. The topics were based on the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2016).¹⁵ and the KDIGO care bundles.¹⁶ Moreover, the monitoring and therapeutic recommendations and treatment targets for resuscitation, antimicrobial therapy, vasoactive medications, RRT, fluid responsiveness assessments were addressed.^{15,16} (see Table 1). In addition, the identification of electronic warnings. The third phase was the Post CERTAIN stage (September 1st, 2016 to February 28th, 2017). In this phase, the medical staff used CERTAIN daily to select patients with septic shock and applied KDIGO care bundles to evaluate and treat patients with septic shock. The last phase was the follow-up phase (March 1st, 2017 to June 1st, 2017). All enrolled patients were tracked for 3 months after hospital discharge to monitor their prognosis and acute and chronic adverse events.

Outcomes

The primary outcome was the incidence and severity of AKI according to the KDIGO 2012 guidelines (see Table 2) within 72h after enrollment. The secondary outcomes included the number of days free of RRT; the numbers of ventilator-free and vasoactive-free days;¹⁷ 90-day all-cause mortality; the length of hospitalization and time of hospitalization-free days at 90 days after discharge; the proportion of patients with major adverse kidney events (MAKES), which was defined as death, dependence on renal replacement therapy (RRT), or a sustained reduction in kidney function at 90 days after discharge (i.e., an estimated glomerular filtration rate [eGFR] of < 75% of the baseline value).¹⁸

Table 1
Recommendations of sepsis and KDIGO care bundles^{15,16}

Items	
Initial resuscitation	30mL/kg of crystalloid fluid is given within the first 3 hours for hypotension or lactate $\geq$ 4mmol/L
Antibiotics	Use broad-spectrum antibiotics within 3 hours and obtain blood culture; daily assessment for de-escalation of antimicrobial therapy
Vasoactive agents	Noradrenaline as the first choice
Fluid response evaluation	200-500mL of crystalloid fluid be given within 10-15minutes, CO or SV increased by 10%-15% [†] , CVP < 5mmHg
The Goal of resuscitation for 6h	MAP $\geq$ 65mmHg; Lactate < 2.0mmol/L; CVP 6-9mmHg; Urine output > 0.5mL/(h·kg)
Stop of ACEi and ARBs	
Renal replacement therapy	PH < 7.1; K ⁺ > 6.5mmol/L; KDIGO 3; Fluid overload
Adjustment of drug doses according to eGFR	
Avoidance of hyperglycemia	Blood glucose levels $\leq$ 150mg/dL or $\leq$ 8.3mmol/L
Avoid nephrotoxic drugs and contrast agents	
†: Transthoracic cardiac ultrasound was used to detect cardiac output (CO) or stroke volume (SV)	
MAP: mean arterial pressure; ACEi: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker	

Statistical analysis

Data were analyzed using SPSS version 18.0 software (IBM Corporation, USA). Normally continuous variables were summarized using the means $\pm$ SDs and were analyzed with the Student's t-test. Non-normal distribution parameters were presented as the medians and interquartile ranges (IQRs) and were analyzed with the nonparametric test. Categorical variables were summarized as numbers (%). The Mann-Whitney test or Fisher's exact test was used for two-group comparisons of categorical variables. Two-sided *P* values less than 0.05 were considered statistically significant in the final analyses.

Table 2
Staging of AKI according to the KDIGO 2012¹⁶

Stage	Serum creatinine	Urine output
1	1.5 to 1.9 times baseline or ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/l}$) increase	< 0.5 ml/kg/hour for 6 to 12 hours
2	2.0 to 2.9 times baseline	< 0.5 ml/kg/hour ≥ 12 hours
3	3.0 times baseline or increase in serum creatinine to ≥ 4.0 mg/dL (≥ 353.6 $\mu\text{mol/L}$) or the initiation of renal replacement therapy	< 0.3 ml/kg/hour ≥ 24 hours or anuria ≥ 12 hours

Results

Baseline characteristics

From January 1st, 2016, to June 1st, 2017, 250 patients were included in the study. Of these enrolled patients, 133 patients were included in the Post-CERTAIN group, and 117 patients were included in the Pre-CERTAIN group. Fourteen patients were excluded, 9 (6.8%) of whom were in the Post-CERTAIN group and 5 (4.3%) of whom were in the Pre-CERTAIN group. In the Post-CERTAIN group, 5 (3.8%) patients withdrew consent, and 4 (3.0%) were lost to follow-up. In the Pre-CERTAIN group, 5 (4.3%) patients were lost to follow-up. Thus, 236 patients (124 in the Post-CERTAIN group and 112 in the Pre-CERTAIN group) were included in the final analysis (Fig. 1). The baseline characteristics of patients in the Pre-CERTAIN group and Post-CERTAIN group are summarized in Table 3. There were no significant differences in age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, comorbidities, site of infection ($P > 0.05$).

Measures during the evaluation period for Pre versus Post CERTAIN application

In the Post-CERTAIN group, both the ratio of fluid response evaluation before fluid resuscitation and 30mL/kg of crystalloid fluid was given within the first 3 hours for early resuscitation was higher than that in the Pre-CERTAIN group (100% vs 48.2% $P < 0.001$, 100% vs 60.7% $P < 0.001$, respectively). The daily fluid balance for day 1 was higher in the Post-CERTAIN group (3180 mL vs 1715 mL, $P < 0.001$). However, fluid balance on day 2 was lower in the Post-CERTAIN group (777.5 mL vs 1275mL, $P = 0.002$). Furthermore, the use of noradrenaline was significantly higher in the Post-CERTAIN group, but significantly patients in Pre- CERTAIN group received dopamine ($P < 0.001$). Compared to the Pre-CERTAIN group, the mean arterial pressure (MAP) of the patients in Post-CERTAIN group significantly increased during the first 6 hours after enrollment (Table 4). In contrast, the level of lactate during the first 12 hours was significantly decreased in the Post-CERTAIN group (Table 4). In addition, the use of the nephrotoxic drug was significantly reduced in the Post-CERTAIN group ($P < 0.001$).

Table 3
Characteristics of the participants at baseline

Characteristic	Pre-CERTAIN	Post-CERTAIN	<i>P</i> -value
	(N = 112)	(N = 124)	
Age (years), mean $\pm$ SD	60.8 $\pm$ 15.2	57.6 $\pm$ 15.9	0.122
Male sex, <i>n</i> (%)	67(59.8%)	73(58.9%)	0.895
APACHE II, mean $\pm$ SD	23.6 $\pm$ 5.1	22.9 $\pm$ 4.7	0.306
SOFA, mean $\pm$ SD	8.3 $\pm$ 2.4	8.2 $\pm$ 2.1	0.798
Comorbidities			
Coronary heart disease, <i>n</i> (%)	82(45.6)	98(54.4)	0.358
Hypertension, <i>n</i> (%)	83(46.4)	96(53.6)	0.648
COPD, <i>n</i> (%)	45(43.7)	58(56.3)	0.358
Diabetes mellitus, <i>n</i> (%)	67(53.2)	59(46.8)	0.068
Stroke, <i>n</i> (%)	37(49.3)	38(50.7)	0.780
Malignancy, <i>n</i> (%)	24(43.6)	31(56.4)	0.541
Immunosuppression, <i>n</i> (%)	50(43.1)	66(56.9)	0.195
Site of infection			
Pulmonary, <i>n</i> (%)	45(40.2)	56(45.2)	0.510
Abdomen, <i>n</i> (%)	31(27.7)	26(21.0)	0.286
Urinary system, <i>n</i> (%)	18(16.1)	24(19.4)	0.610
Bloodstream, <i>n</i> (%)	6(5.4)	11(8.9)	0.326
Skin and soft tissue, <i>n</i> (%)	8(7.1)	7(5.6)	0.791

Table 4
Measures within 72h after enrollment

Parameters	Pre-CERTAIN	Post-CERTAIN	P-value
	n = 112	n = 124	
Fluid response evaluation	54(48.2)	124(100)	< 0.001***
Initial resuscitation	68(60.7)	124(100)	< 0.001***
Fluid balance (ml), IQR			
Day 1	1715(666.3–2680)	3180(2500–3900)	< 0.001***
Day 2	1575(100–2685)	1175(160–2370)	0.674
Day 3	1275(-52.5–2398)	777.5(-250–1380)	0.002**
Vasoactive agents			
Noradrenaline	72(64.3)	124(100)	< 0.001***
Dopamine	46(41.1)	0	< 0.001***
Dobutamine	15(13.4)	25(20.2)	0.224
Vasopressin	5(4.5)	20(16.1)	0.005**
MAP, mean (± SD)			
0h	55(4.5)	54(4.0)	0.517
1h	62(7.4)	74(6.5)	< 0.001***
3h	70(7.1)	75(4.7)	0.003**
6h	77(5.1)	82(5.6)	0.003**
12h	81(5.5)	83(4.8)	0.176
24h	79(5.4)	81(5.3)	0.193
Lactate, mean (± SD)			
0h	6.0(2.08)	6.2(2.01)	0.742

Parameters	Pre-CERTAIN	Post-CERTAIN	<i>P</i> -value
	n = 112	n = 124	
3h	5.6(1.47)	4.7(1.47)	0.017**
6h	2.5(0.74)	2.2(0.50)	0.025**
12h	1.2(0.40)	1.0(0.34)	0.025**
24h	0.9(0.35)	0.9(0.36)	0.749
Broad-spectrum antibiotics	100(89.3)	124(100)	< 0.001***
Blood culture obtained	88(78.6)	124(100)	< 0.001***
Assessment for de-escalation of antimicrobial therapy	74(66.1)	124(100)	< 0.001***
Hyperglycaemia	0	0	
Nephrotoxic drug	16(14.3)	0	< 0.001***

Primary And Secondary Outcomes

The occurrence of AKI within 72h after enrollment was lower in the Post-CERTAIN group than the Pre-CERTAIN group (55.7% vs 68.8%, $P = 0.045$). According to the KDIGO classification system, moderate to severe AKI occurred in significantly fewer patients in the Post-CERTAIN group compared to the Pre-CERTAIN group (32.3% vs 46.4%, $P = 0.032$). In the Post-CERTAIN group, significantly lower rates of moderate to severe AKI were observed compared to the Pre-CERTAIN group at discharge (25.8% vs 39.3%, $P = 0.036$). Patients in the Post-CERTAIN group had much longer ventilator-free days and vasoactive-free days (22 vs 17, $P < 0.001$; 23 vs 19, $P = 0.044$, respectively). Patients in the Post-CERTAIN group had a shorter ICU stay than those in the Pre-CERTAIN group ($P = 0.003$). Patients in the two groups had similar duration of hospitalization and in-hospital mortality. (Table 3). However, the difference in 90-day mortality was marked lower in the Post-CERTAIN group than the Pre-CERTAIN group (17.7% vs 29.5%, $P = 0.045$). The proportion of patients with MAKES in the Post-CERTAIN group was lower than that in the Pre-CERTAIN group (41.9% vs 56.3%, $P = 0.039$). Patients in the Post-CERTAIN group had a similar rate of RRT dependence and re-hospitalization at 90 days (Table 5).

Table 5
Primary and secondary outcomes

	Pre-CERTAIN	Post-CERTAIN	<i>P</i> -value
Primary outcome			
AKI occurrence within 72h after enrollment	77(68.8)	69(55.7)	0.045*
AKI stage within 72h after enrollment			0.032*
KDIGO stage 0/1, <i>n</i> (%)	60(53.6)	84(67.7)	
KDIGO stage 2/3, <i>n</i> (%)	52(46.4)	40(32.3)	
Secondary outcomes			
AKI stage at discharge			0.036*
KDIGO stage 0/1, <i>n</i> (%)	68(60.7)	92(74.2)	
KDIGO stage 2/3, <i>n</i> (%)	44(39.3)	32(25.8)	
Median no. of ventilator-free days at 28 days (IQR)	17(0–23)	22(21–23)	< 0.001***
Median no. of days free from vasoactive agents at 28 days (IQR)	19(0–20)	23(0–25)	0.044*
Length of ICU stay, days	10(6–21)	10(6–13)	0.003**
Length of hospital stay, days	17.5(12–22)	17(14–22)	0.764
In-hospital mortality, <i>n</i> (%)	28/112(25.0)	19/124 (15.3)	0.073
RRT dependence at 90 days, <i>n</i> (%) [‡]	15/79 (19.0)	22/102 (21.6)	0.713
MAKES at 90 days, <i>n</i> (%)	63/112 (56.3)	52/124 (41.9)	0.039*
Death from any cause at 90 days, <i>n</i> (%)	33/112 (29.5)	22/124 (17.7)	0.045*
Re-hospitalization at 90 days, <i>n</i> (%) [‡]	8/79 (10.1)	9/102 (8.8)	0.801
[‡] : The number of patients still alive at 90 days was 79 in the Pre-CERTAIN group and 102 in the Post-CERTAIN group.* <i>P</i> < 0.05; ** <i>P</i> < 0.01; *** <i>P</i> < 0.01			

Discussion

In this before-and-after study, we examined whether CERTAIN based on sepsis and KDIGO care bundles targeted at prevention of AKI on patients with septic shock. This study showed that the use of CERTAIN as a screening and treating tool reduced the ratio of AKI in patients with septic shock, especially the rate of moderate to severe AKI in the Post-CERTAIN group. Moreover, the patients who were managed with CERTAIN had a lower proportion of mortality and rate of MAKEs within 90 days.

Whether KDIGO care bundles improve the short or long outcomes of critically ill patients is inconsistent due to the heterogeneity of AKI. Previously, Koeze et al. discovered that care bundles focusing on KDIGO 2012 had no beneficial effect on critically ill patients when evaluated the ICU mortality, RRT dependency, and AKI progression.¹⁹ However, our data indicated that implementation of CERTAIN focusing on sepsis 3.0 and KDIGO bundles can reduce the occurrence of AKI, mortality, and incidence of MAKEs within 90 days of patients with septic shock. These results are consistent with the studies that evaluated KDIGO care bundles in patients after cardiac surgery and major surgery.^{14,20,21}

It is noteworthy that the implementation of the Surviving Sepsis Campaign and KDIGO care bundles improved the short- and long-term outcomes of sepsis and AKI, respectively.^{22, 23} However, in clinical practice, these interventions have been shown to have poor performance. Bundle fatigue was one of the main issues affecting their implementation.²⁴ Moreover, in the absence of sufficient support for decision making and the inappropriate selection of medical interventions, medical errors are the leading cause of death in hospitals.^{25, 26} In this study, CERTAIN was associated with improvement of eight of 10 practices of the KDIGO care bundles. The compliance of the crucial practices may influence the prognosis of the patients, as the higher adherence to active measures has been shown great benefits of care bundles.²⁷ Recently, a multicentre international study showed that CERTAIN improved daily care processes in ICU, especially in low- and middle-income countries.²⁸ Care bundles in the form of a list combined with an electronic warning could improve the compliance of medical staff to evidence-based guidelines, minimize medical errors and improve outcomes in ICU.²⁹ The high adherence of care bundles after CERTAIN training was associated with improvement in the treatment of patients with septic shock.

Fluid resuscitation and vasoactive agents are cornerstones in the treatment of both septic shock and AKI.^{15, 16} Fluid challenge should be evaluated between the balance of increasing in oxygen delivery to tissues and inhibiting of edema formation.³⁰ In contrast to the Pre-CERTAIN group, all the patients in the Post-CERTAIN group were evaluated for fluid responsiveness, then monitored CVP during the following fluid management. CVP is not an accurate indicator to predict fluid responsiveness, but CVP is the most frequently used and most easily obtained variable to guide fluid resuscitation in ICU.³¹ Single CVP value cannot differentiate responder from nonresponder. However, the changing of CVP during fluid bolus may predict responsiveness. Thus, patients in the Post-CERTAIN group were given 200-500mL crystalloid fluid within 10–15 minutes. If CO and SV detected by transthoracic Doppler increased by 10%-15% with a rise in CVP < 5mmHg indicates good tolerance to fluids, whereas an increase in CVP $\geq$ 5mmHg indicates poor tolerance to fluids.³¹ To inhibit delayed resuscitation and fluid overload, this study used changes in CVP during fluid challenge together with changes in CO to predict fluid responsiveness.³¹ In addition, CVP

maintained to 8-12mmHg as the following target as the majority of patients respond to fluids.³² The increased use of noradrenaline and de-escalation fluid resuscitation in the Post-CERTAIN group maintained a better haemodynamic stabilization and tissue perfusion.

The pathophysiology of SA-AKI is complicated. Surviving Sepsis Campaign care bundles showed no reduction in the incidence of AKI within the first week after the development of sepsis.³³ We implemented a bundle of supportive measures which are recommended by sepsis and KDIGO guidelines. The multifactorial measures may reduce the occurrence of AKI after septic shock. SA-AKI is associated with increased morbidity and mortality. Our findings were in line with goal-directed therapy in a reduction of mortality and MAKEs.³⁴ However, the PreAKI study showed that the implementation of the KDIGO guidelines had no impact on mortality and MAKEs at day 90. That might be due to the different eligible patients. We assumed that the positive effect of the CERTAIN checklist on reducing the incidence and severity of AKI, decrease in mortality, and MAKEs at day 90 was caused by optimal fluid resuscitation with de-escalation fluid management and kidney protection.

Our study has several limitations. First, it was a single-center study of patients with septic shock may limit the generalizability of its results. Second, this study was not blinded, which resulted in measurement bias. Third, the Hawthorne effect was the confounding factor in before-after studies. Further trials with a larger multicenter cohort of patients with septic shock are warranted.

Conclusions

To our knowledge, this is the first report of the use of CERTAIN based on sepsis 3.0 and KDIGO care bundles in septic shock patients. This trial showed that the application of CERTAIN can decrease the occurrence of AKI in patients with septic shock. Moreover, CERTAIN can decrease the mortality and rate of MAKEs at 90 days after exposure to sepsis.

List Of Abbreviations

AKI

acute kidney injury

CERTAIN

Checklist for Early Recognition and Treatment of Acute Illness

KDIGO

Kidney Disease:Improving Global Outcomes

MAKEs

major adverse kidney events

CKD

chronic kidney disease

ICU

intensive care unit

SA-AKI

sepsis-associated acute kidney injury

RRT

renal replacement therapy

eGFR

estimated glomerular filtration rate

IQR

medians and interquartile ranges

MAP

mean arterial pressure

CVP

central venous pressure

Declarations

Ethics approval and consent to participate: The clinical trial was found to be in accordance with the ethical principles and the national norms and standards for conducting medical research in China. The study protocol was approved by the Ethics Committee of the Hospital of Tianjin First Center Hospital (approval No 2015KZ019). All the patients or their authorized representatives have written informed consent.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Competing interests: All the authors declare that they have no competing interests.

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Authors' contributions: L.D. and J.J.W. designed the experiment; J.J.W., L.D., H.M.G., Y.Q.W. collected data; J.L. analyzed data; J.J.W. wrote the manuscript; H.M.G. edited the manuscript. L.D. and H.M.G. were the guarantors of this work and took responsibility for the contents of the article. All authors have contributed significantly and agree with the content of the manuscript.

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Figures

Figure 1

Study flow diagram