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Elevated arterial lactate level as an independent risk factor for pancreatic infection in moderately severe acute pancreatitis

Wenqing Shu [1], Jianhua Wan [1], Jie Chen, Wenhua He, Yin Zhu, Nonghua Lu, Liang Xia*

Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang, PR China

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ABSTRACT

Purpose: The present study aimed to research the relationships between arterial lactate levels and pancreatic infection in moderately severe acute pancreatitis.
Methods: This study retrospectively analyzed data from 503 patients with moderately severe acute pancreatitis from January 1, 2013, to March 31, 2018. The baseline characteristics on admission were compared between patients with and without elevated arterial lactate levels. The parameters and laboratory data were compared between patients with and without pancreatic infections at admission. Univariate and multivariate logistic regression analyses were used to assess the value of elevated arterial lactate levels for identifying high-risk patients. $P \leq 0.05$ was considered statistically significant.
Results: A total of 49 (9.2%) patients were diagnosed with pancreatic infections. Compared with patients without pancreatic infections, pancreatic infection patients had significantly increased arterial lactate levels at admission (1.5 ± 0.7 vs. 2.5 ± 0.9; $P < 0.01$). Multivariate logic analysis still showed that higher arterial lactate levels in moderately severe acute pancreatitis was an independent risk factor for developing pancreatic infections (hazard ratio: 6.31, 95% CI 3.01−13.24; $P < 0.01$). Arterial lactate level $\geq$2.1 mmol/L and procalcitonin level $\geq$0.5 ng/mL at admission had area under the receiver operating characteristic curves of 0.83 and 0.72, with sensitivity of 67.2% and 87%, and specificity of 82.0% and 60%, respectively, for the prediction of pancreatic infection in moderately severe acute pancreatitis.
Conclusions: Our results indicate that a higher arterial lactate level is independently associated with pancreatic infection in patients with moderately severe acute pancreatitis and may be used as a tool to identify high-risk patients.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas, which can lead to problems ranging from local complications to systemic inflammatory response, organ failure and even death. AP is typically classified into three degrees of severity: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP), according to the new 2012 revision of the Atlanta Classification [1]. Almost all patients who suffer from MAP have a good outcome. An important significance of the new revision is that patients with MSAP may resolve their pancreatitis without intervention and aggressive treatment. However, some patients will progress to pancreatic infection (PI), which is a fatal complication and they will need active intervention or to be transferred for specialist care. If clinicians can identify the high-risk groups and low-risk groups early, they can save medical resources, reduce patient costs and potentially improve patient outcomes. Therefore, early identification of the risk of PI is critical in patients with MSAP because early proper treatment and intervention (such as enteral nutrition [2,3] and use of antibiotics [4,5]) may improve the prognosis and reduce mortality in these patients.

Abbreviations: MSAP, moderately severe acute pancreatitis; PI, pancreatic infection; AP, acute pancreatitis; MAP, mild acute pancreatitis; AUC, area under curve; ROC, receiver operating characteristic; HR, hazard ratio; ICU, intensive care unit; SAP, severe acute pancreatitis; CRP, C-reactive protein; PCT, procalcitonin; SD, standard derivation; CI, confidence interval; RCT, randomized controlled trial; and BUN, blood urea nitrogen.

* Corresponding author. Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, 17 Yongwaizheng Street, Nanchang, Jiangxi, 330006, PR China.
E-mail addresses: 15170428125@163.com (W. Shu), 18942337437@163.com (J. Wan), 18270916863@163.com (J. Chen), hewenhua@126.com (W. He), zhuyin27@sina.com (Y. Zhu), lunonghua@ncu.edu.cn (N. Lu), xialiang79@163.com (L. Xia).
[1] Denotes Equal Contribution of First Authors.

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Previous studies have shown that elevated levels of a number of serum markers are closely related to the severity of AP, including C-reactive protein (CRP), procalcitonin (PCT), white blood cells, blood urea nitrogen (BUN), and serum creatinine, as well as age and hemoconcentration. Some of these factors have also been reported as indicators of PI. However, most of the research only involved SAP rather than MSAP, and the results were not satisfactory, so we need to find new markers. Lactate is one of the byproducts of glycolysis of glucose under anaerobic conditions and is considered an important indicator to reflect ischemia and hypoxia in tissue. Lactate levels can also be elevated in during infections. Some studies have demonstrated that an elevated lactate level is an established marker of bacterial infection in other diseases [6–9]. In addition, a recent study has shown that an elevated lactate level is closely related to persistent organ failure in AP [10], but no study has reported specifically on the relationship between elevated lactate levels and PI in MSAP.

Materials and methods

Definitions

The diagnosis of AP was based on the presence of two or more of the following three criteria: (1) classic abdominal pain; (2) elevation of serum amylase and/or lipase level to three times the upper limit of the normal range; and (3) computed tomography findings characteristic of AP [1]. MSAP was diagnosed by the presence of transient organ failure or local or systematic complications in the absence of persistent organ failure. Organ failure included the cardiovascular, pulmonary, and/or renal systems and was defined as the following parameters: a systolic blood pressure <90 mm Hg that persisted following fluid resuscitation; an arterial $PO_2 < 60$ mm Hg on room air or requirement for mechanical ventilation; and/or a serum creatinine level ≥2 mg/dl after rehydration or need for hemodialysis in patients without preexisting renal disease [1]. Transient organ failure was defined when the conditions lasted for less than 48 h. The diagnosis of pancreatic infection was based on typical imaging criteria in patients with persistent peripancreatic gas collections when contrast-enhanced computed tomography or a fine-needle aspiration was positive for bacteria and/or fungi on a gram stain and culture [1]. The diagnosis of acute peripancreatic fluid collection must conform with the following CT criteria: occurred in the setting of interstitial edematous pancreatitis; was a homogeneous collection with fluid density; did not have a defined wall; confined by normal peripancreatic fascial planes; and was adjacent to the pancreas. Pancreatic necrosis was diagnosed based on the following contrast-enhanced CT criteria: presence of findings indicating peripancreatic necrosis and/or lack of pancreatic parenchymal enhancement by an intravenous contrast agent. A biliary AP diagnosis was required to meet any of the following criteria in patients with AP: high transaminase and/or bilirubin; and bile duct stone or dilation demonstrated by abdominal US, CT, ERCP or MRCP. A diagnosis of hyperlipidemic AP was required to meet the following criteria in patients with AP: triglycerides ≥11.30 mmol/L and the exclusion of other etiologies of AP. An alcohol AP diagnosis was required to meet the following criteria in patients with AP: a clear abnormal alcohol intake before the attack of AP; alcohol intake>50 g/d for a duration >5 years; and the exclusion of other etiologies. A diagnosis of idiopathic AP was required to must meet the following criterion in patients with AP: the exclusion of all of our known etiologies of the disease.

Patients

This study included consecutive adults diagnosed with AP from January 2013 to March 2018 at the First Affiliated Hospital of Nanchang University. Patients were required to meet the following criteria: first diagnosis of AP; time from abdominal pain onset to hospital admission ≤72 h; age 18 years and over; arterial lactate levels tested within 2 h after hospitalization and other blood samples measured within 24 h; and had a complete medical record. The outcomes are PI and in-hospital mortality. The reference values of arterial lactate levels with this assay are 0.9–1.6 mmol/L. The reference values for the white blood count, BUN level, serum creatinine level, hemoconcentration, PCT level and CRP level with this assay are $3.5–9.5 \times 10^9$/L, 2.6–7.5 mmol/L, 41–75 μmol/L, 40–50%, less than 0.5 ng/ml and less than 10 mg/L, respectively. The ethics review board of The First Affiliated Hospital of Nanchang University approved this study (No. 2011001).

Statistical analysis

Statistical analysis was performed using IBM SPSS software, version 19.0 (SPSS, Chicago, USA). Continuous data were analyzed by Student's t-tests and Mann-Whitney U tests and are presented as the means and standard derivation (SD). Chi-square tests were used to analyze categorical variable, which are reported as the number (frequency). The receiver operating characteristic (ROC) curve, sensitivity, specificity and area under the curve (AUC) were measured to evaluate the value of arterial lactate levels in predicting secondary infections of MSAP. All indicators were further tested with univariate and multivariate logistic regression analyses. Multivariate analysis was performed with a Cox regression model. The hazard ratio (HR) and 95% confidence intervals (95% CIs) are shown. A P value ≤ 0.05 was considered statistically significant.

Results

Comparison between patients with different arterial lactate levels

In this study, we included 503 patients with confirmed MSAP. The baseline characteristics of these patients based on arterial lactate levels shown in Table 1. The mean age of patients with normal or low arterial lactate levels was 50.7 years, and 55.8% of the patients were male. The mean age of patients with elevated arterial lactate levels was 49.1 years, and 62% of the patients were male. The mean age was different between the normal or low group and the elevated group (52.4 ± 15.7 vs. 49.1 ± 2.9; P = 0.02), but the elevated group was younger. No significant differences were observed in sex or etiology. Compared with the normal or lower arterial lactate group (N = 319), patients with elevated arterial lactate levels (N = 184) have a significantly higher chance to develop PIs (21.1% 3.1%; P < 0.01), develop pancreatic necrosis (57.1% 13.7%; P < 0.01), need a longer hospitalization stay (13.8 ± 9.5 vs. 10.0 ± 4.9; P < 0.01), need a longer hospitalization stay in the ICU (4.45 ± 8.8 vs. 1.5 ± 2.9; P < 0. 01), and experience in-hospital mortality (2.7% vs. 0.3%; P = 0.03). In contrast, patients with a normal arterial lactate level have a higher chance for acute peripancreatic fluid collection (71.6% 42.9%; P < 0.01), which is a minor complication.

Comparison between patients with and without PI

As shown in Table 2. Approximately 9.2% of patients (N = 49) were identified with PIs in MSAP, and 12.2% of patients (N = 6) died in the hospital. We did not observe deaths in patients without PIs before discharge. Compared to patients without PIs, patients with PIs had more bad outcomes, such as longer hospital stays (24.8 ± 12.7 vs. 10.0 ± 4.4; P < 0.01), longer hospital stays in the ICU (12.6 ± 13.5 vs. 1.5 ± 2.8; P < 0.01), and even higher in-hospital

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Table 1
Basic characteristic of MSAP patients according to arterial lactate level (normal range < 1.6 mmol/L).

Variables	arterial lactate ≤1.6 mmol/L N = 319	arterial lactate >1.6 mmol/L N = 184	P-value
Ages, years	52.4 ± 15.7	49.1 ± 15.1	0.02
Male gender	178(55.8%)	114(62.0%)	0.19
Etiology			0.06
Biliary	207(64.9%)	99(54.8%)	
Alcohol	28(8.8%)	18(9.8%)	
Hypertriglyceridemia	74(23.2%)	62(33.7%)	
Idiopathic	10(3.1%)	5 (2.7%)	
Outcome			
PI	10(3.1%)	39(21.1%)	<0.01
Hospital stay	10.0 ± 4.9	13.8 ± 9.5	<0.01
Hospital stay in ICU	1.5 ± 2.9	4.4 ± 8.8	<0.01
In-hospital mortality	1(0.3%)	5(2.7%)	0.03

Abbreviations: MSAP, moderately severe acute pancreatitis; ICU, intensive care unit; AL, PI, pancreatic infection.

Table 2
Clinical data of the patients with and without PI.

Variables	All patients N = 503	Non-PI N = 454(90.8%)	PI N = 49(9.2%)	P-value
Ages, years	51.2 ± 15.5	51.5 ± 15.8	48.4 ± 12.3	0.19
Male gender	259	33		0.17
Etiology				0.28
Biliary	306(60.9%)	279(61.5%)	27(55.1%)	
Alcohol	46(9.1%)	39(8.6%)	7(14.3%)	
Hypertriglyceridemia	136(27.0%)	124(27.3%)	12(24.5%)	
Idiopathic	15(3.0%)	12(2.6%)	3(6.1%)	
Laboratory data				
White blood count($\times 10^9$/L)	14.1 ± 5.2	14.0 ± 5.3	15.1 ± 5.1	0.14
BUN (mmol/L)	5.8 ± 3.3	5.7 ± 3.3	6.6 ± 3.2	0.06
Serum creatinine (μmol/L)	69.8 ± 29.5	68.7 ± 28.4	80.3 ± 37.2	0.03
Hemoconcentration (%)	41.4 ± 6.5	41.0 ± 6.3	44.7 ± 7.6	<0.01
Hematocrit ≥44, n (%)	176(33%)	150(33%)	26(53%)	<0.01
PCT (ng/ml)	3.2 ± 8.1	3.1 ± 8.3	4.4 ± 6.2	<0.01
CRP (mg/L)	177.3 ± 117.0	170.1 ± 114.9	244.2 ± 116.2	<0.01
Arterial lactate (mmol/L)	1.7 ± 0.8	1.5 ± 0.7	2.5 ± 0.9	<0.01
Severity scores				
SIRS scores ≥3, n (%)	64(12.7.0%)	50(11.0.0%)	14(28.5.0%)	<0.01
APACHEIIscore≥8, n (%)	170(33.8.0%)	150(33.0.0%)	20(40.8.0%)	0.27
Outcome				
APNC, n (%)	346(68.8.%)	325(71.6.%)	21(42.9.%)	<0.01
Pancreatic necrosis, n (%)	90(17.9%)	62(13.7%)	28(57.1%)	<0.01
Hospital stay, days	11.4 ± 15.5	10.0 ± 4.4	24.8 ± 12.7	<0.01
Hospital stay in ICU,days	2.5 ± 6.0	1.5 ± 2.8	12.6 ± 13.5	<0.01
In-hospital mortality	6(1.2%)	0(0%)	6(12.2%)	<0.01

Abbreviations; ICU, intensive care unit; PI, pancreatic infection, CRP, C- reactive protein, PCT, procalcitonin, BUN, blood urea nitrogen, Acute peripancreatic fluid collection.

mortality (12.2% vs. 0%; P < 0.01). The differences in age, sex, etiology, white blood count and BUN level were not statistically significant between patients with and without PIs. Although the elevated levels of conventional biomarkers, including PCT, CRP, and serum creatinine, as well as hemoconcentration were significantly higher in patients with PI, the level of arterial lactate (AL) still was significantly different (1.5 ± 0.7 vs. 2.5 ± 0.9; P < 0.01).

Arterial lactate as an independent risk factor for PI

As shown in Table 3, to further investigate the association between arterial lactate levels and the incidence of PI, we performed univariate and multivariate logistic regression analyses on all laboratory data and age (≥60 years). We found that arterial lactate levels ≥2.1 mmol/L (HR: 6.31, 95% CI 3.01−13.24; P < 0.01) and PCT

Table 3
Uni- and multi-variate logistic regression analyses of risk factors for PI.

Variables	Univariate analysis Hazard ratio (95%CI)	P-value	Multivariate analysis Hazard ratio (95%CI)	P-value
Ages≥60 years	0.44 (0.20, 0.96)	0.04	0.51 (0.22, 1.19)	0.12
White blood count≥16 $\times 10^9$/L	1.89 (1.04,3.42)	0.04	1.31 (0.68, 2.52)	0.42
Serum creatinine≥133μmol/L	3.33 (1.15, 9.59)	0.03	1.90 (0.59, 6.17)	0.29
Hemoconcentration≥44%	3.33 (1.40, 4.60)	0.02	1.21 (0.62, 2.38)	0.55
PCT≥0.5 ng/ml	7.17 (2.79, 18.43)	<0.01	4.36 (1.61, 11.84)	0. 04
CRP≥150 mg/L	3.50 (1.75, 7.02)	<0.01	1.97 (0.92, 4.23)	0.08
arterial lactate≥2.1 mmol/L	8.31 (4.03, 17.11)	<0.01	6.31 (3.01, 13.24)	<0.01

Abbreviations; AL, arterial lactate; PI, pancreatic infection, CRP, C- reactive protein, PCT, procalcitonin.

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levels ≥0.5 ng/ml (HR: 4.36, 95% CI 1.61–11.84; P = 0.04) were independent risk factors for PI. As shown in Fig. 1, an arterial lactate level ≥2.1 mmol/L and procalcitonin level ≥ 0.5ng/mL on admission for the prediction of PI in MSAP had AUC of 0.83 (95% CI: 0.78–0.88) and 0.72 (95% CI: 0.66–0.79), with sensitivity of 67.2% and specificity 87%, and sensitivity of 82% and specificity 60%, respectively.

Discussion

In the present study, to determine the cutoff value of lactic acid, we must first use AUC, sensitivity, and specificity to evaluate the value of predicting PIs in MSAP. In this research, we found that the arterial lactate level may be a simple, repeatable, available and important tool in predicting PIs in MSAP on admission, and we also suggested that elevated arterial lactate and PCT levels are independent risk factors for secondary infection in MSAP, as defined by the latest classification system.

AP is still a clinical challenge. Although the management of AP has improved over the years, the overall population mortality rate for AP in the United States has remained unchanged [11]. According to previous studies, spontaneous infections in necrotic pancreas and peripancreatic collections are one of the major factors affecting AP mortality [12,13]. Therefore, the ability to identify MSAP patients at risk for developing PIs at an early stage is critical. We still lack the ideal early predictors. In recent years, CRP and PCT levels have been reported to be predictors of the development of PIs in AP [14–16]. However, these studies had some common limitations. First, their sample size was relatively small (N < 200). The cutoff values for CRP and PCT levels in these studies had relatively larger range. Furthermore, their outcomes may produce large deviations due to the use of old diagnostic criteria, because the new criteria found that infected necrosis is rare during the first week [1]. Therefore, we need simple, economically measured and promising clinical parameters.

As we mentioned above, the lactate level may be a simple, inexpensive, repeatable, potential clinical biochemical indicator for the assessment of primary PIs in patients with MSAP. Many studies have reported that an elevated level of lactate was a predictor of poor outcomes in many serious infectious conditions [8,17,18]. Mikkelsen et al. showed that the initial serum lactate level was associated with mortality independent of clinically apparent organ dysfunction and shock in patients admitted to the emergency department with severe sepsis [17]. A prospective study by Trzeciak et al. suggested that the mortality rate in infected patients is closely related to the initial level of serum lactate [18]. In their study, the in-hospital mortality was 15%, 25%, and 38% in the low, intermediate, and high lactate groups, respectively. Furthermore, Freund et al. pointed out that the levels of lactate and PCT were complementary for the diagnosis and risk-stratification of patients evaluated in the emergency department for suspected infection [8]. As the most serious complication of AP, persistent organ failure and PIs are responsible for the main causes of death in the early and late stages of AP, respectively. Thus, all of these findings imply that elevated lactate levels may be associated with persistent organ failure, PIs and even death in AP.

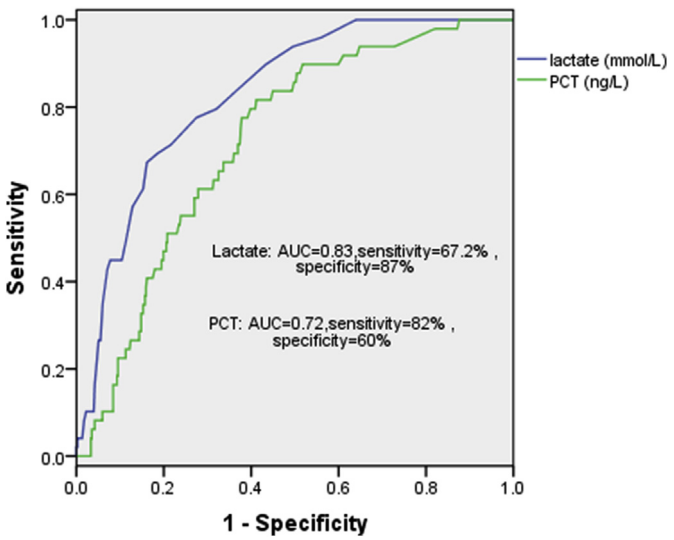

Fig. 1. AUC, sensitivity, specificity of arterial lactate and PCT on admission in predicting pancreatic infection.

In 2017, Valverde-Lopez et al. first described that serum lactate levels could be useful for developing new scores for predicting severe acute pancreatitis with an AUC of 0.79 and predicting death with an excellent AUC of 0.8710. Our findings support the conjecture that patients with high arterial lactate levels show significantly higher incidences of developing PIs (P < 0.01) and experiencing death (P = 0.03) compared with those with normal lactate levels in MSAP. Several possible explanations exist for this hypothesis. First, an elevated lactic acid level is one of the important indicators for ischemia and hypoxia of the body, and the gastrointestinal system is extremely sensitive to ischemia and hypoxia. The destruction of the intestinal barrier and dysfunction caused by ischemia and hypoxia are main mechanisms for the intestinal flora displacement in patients with AP [19]. Based on a large number of experimental studies, pancreatic tissue infection is mainly caused by bacterial translocation from the gut [20–22]. In addition, one theory supports that the serum lactate level is an early biomarker that reflects the severity of systemic inflammatory responses in sepsis [17,23]. However, the immune function was impaired by systemic inflammatory reactions and further impaired the ability to clear bacteria, making pancreatic tissue susceptible to intestinal bacterial infection [24]. Finally, when an infection is present, leukocytes increase anaerobic glucose metabolism, further resulting in the elevation of lactic acid levels [25,26].

In recent years, the association between PCT level and AP infection has been extensively studied [15,16,27]. A systematic review involving seven randomized controlled trials (RCTs) confirmed this finding, and serum procalcitonin measurements may be valuable in predicting the risk of developing infected pancreatic necrosis. In this study, the pooled sensitivity and specificity of PCT levels as a predictor of the development of infected pancreatic necrosis were 0.80 (95% CI = 0.70–0.87) and 0.91 (95% CI = 0.87–0.94), respectively, with an overall AUC of 0.91[27]. Moreover, one multicenter RCT with 104 patients showed that the monitoring of PCT allows early and reliable assessment of clinically relevant pancreatic infections and overall prognosis of AP [15]. Our results are in line with a previous multicenter prospective controlled trial [15] and a systematic review [27].

Based on the above studies and our results, we suggest that arterial lactate and PCT levels can be used as independent risk factors for PIs in MSAP. Our research results showed that a high lactate level was a parameter of poor outcomes in MSAP. With an arterial lactate ≥2.1 mmol/L as the cutoff value, the HR for PIs in MSAP was 6.31 (95% CI 3.01–13.24), surpassing the 4.36 value of PCT (95% CI 1.61–11.84), and the AUC, sensitivity, and specificity values for predicting PIs were 0.83, 67.2%, and 84%, respectively.

This study has several strengths. First, we have provided the largest sample size so far, which can reduce the selection bias. Second, to the best of our knowledge, this is the first study to explore the relationship between AL levels and PI in patients with MSAP, while excluding the effects of different severities. In

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addition, we used univariate and multivariate logistic regression analyses to rule out the effects of other factors, including PCT, CRP and so on.

The limitations of our research include the following: First, selection bias potentially existed in our retrospective study, so we expanded the sample size and adopted strict inclusion criteria to minimize the potential of selection bias. Second, arterial lactate levels were not tested in all patients with MSAP at admission. Third, we did not follow up with the patients after discharge, which may have an impact on our results. Despite the limitations of our study, the results still provide a valuable marker to predict the risk of developing pancreatic infections in MSAP at the early stages.

Conclusion

In conclusion, this single center, retrospective trial showed that the initial AL level is associated with PI and mortality in patients admitted with MSAP. From this perspective, the arterial lactate level may serve as a useful, simple tool to identify high-risk patients for PIs in MSAP. However, further large-scale, prospective, and multicenter studies are needed to confirm our findings.

Disclosure statement

The authors declare no potential conflicts of interest. No writing assistance was provided in the production of this manuscript.

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Wenqing Shu and Jianhua Wan conceived the study; Wenqing Shu, Wenhua He, Yin Zhu, Liang Xia and Nonghua Lu participated in the study design; Wenqing Shu collected the data; Wenqing Shu, Jianhua Wan, and Jie Chen performed the statistical analyses; Jianhua Wan and Wenqing Shu drafted the manuscript; and Liang Xia edited and checked the manuscript. All of the authors have read and approved the final manuscript.

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