Adjuvant rhubarb alleviates organs dysfunction and inhibits inflammation in heat stroke

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Abstract. The aim of the present study was to investigate the effects of adjuvant rhubarb on the recovery of patients with heat stroke. A total of 85 patients with heat stroke were randomly assigned to two treatment groups: One group receiving conventional treatment for heat stroke (conventional group) and one group receiving rhubarb supplement in addition to conventional treatment (rhubarb group). Liver and kidney function parameters, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, plasma interleukin-6 (IL-6), procalcitonin (PCT), C-reactive protein (CRP) levels and venous white blood cell count (WBC) were analyzed. The length of stay in the intensive care units (ICUs) and hospital were recorded. Kaplan-Meier curves were drawn to determine the 30-day survival of the patients. The results indicated that rhubarb supplementation significantly reduced the WBC, as well as CRP, PCT and IL-6 levels at treatment days 3-5. Furthermore, rhubarb intake was observed to limit heat stroke-induced damage to liver and kidney function by decreasing the abnormally high levels of plasma aspartate aminotransferase, alanine aminotransferase and creatinine. Finally, patients in the rhubarb group had shorter ICU and hospital stays as well as a lower APACHE II score than those in the conventional group. However, no significant difference in the 30-day mortality rate was observed between the two groups. In conclusion, rhubarb intake provided a significant benefit for patients with heat stroke by inhibiting systemic inflammation and mitigating liver and kidney injury.

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Introduction

Heat stroke is a severe condition characterized by a core temperature of >40˚C and central nervous system abnormalities, including delirium, convulsions and coma resulting from exposure to environmental heat (classic heat stroke) or strenuous physical exercise (exertional heat stroke) (1). A variety of cytokines are known to be produced in response to endogenous or environmental heat (1,2). Heat stroke is triggered by hyperthermia but is driven by endotoxemia, a condition which triggers a systemic inflammatory response. Such a response may lead to numerous symptoms: Systemic coagulation and hemorrhage, cell death, tissue necrosis, multiple organ dysfunction syndrome or multi-organ failure, including neurological impairment, acute renal failure, disseminated intravascular coagulation, and extensive hepatic and muscle damage (3,4). Despite adequate aggressive hypothermia treatment to lower the body temperature of affected patients, severe heat stroke is usually fatal and those who do survive may suffer permanent nerve damage (5). The systemic progression of the inflammatory response in heat stroke is similar to that occurring in sepsis (6). Chinese rhubarb, also known as Turkey rhubarb, is a plant species of the *Polygonaceae* family that has been used as a herbal medicine for numerous years throughout the world. Chinese rhubarb contains free and binding anthraquinone derivatives, including tannins, two styrene glycosides, naphthol glycosides and benzyl ketones (7). Previous research has indicated that rhubarb has potent anti-inflammatory activity and its active ingredient, rhubarb acid, has been reported to reduce liver and kidney damage (8). Previous studies by our group have indicated that a compound contained in Chinese rhubarb, emodin, inhibits the body's inflammatory response and reduce organ damage from acute pancreatitis or sepsis (9,10). In the present clinical study, rhubarb was administrated as a supplementary treatment for patients with heat stroke. The results demonstrated that administration of rhubarb may inhibit inflammation and protect organ function.

Patients and methods

Patient groups. The present study was performed at the Intensive Care Units (ICUs) of the Affiliated Hospital

of Jiangsu University and Zhenjiang No. 2 Hospital, and the Emergency Department of the Affiliated Hospital of Jiangsu University (Jiangsu, China). The present study was registered with the Chinese Clinical Trial Registry (trial no. ChiCTR1800016460). Critically ill patients with heat stroke were consecutively recruited. Between May 2013 and September 2017, 410 patients were assessed for heat stroke and 85 patients were selected for inclusion in the present study (1). The patients were randomly assigned to one of two groups receiving either conventional heat stroke treatment (conventional group) or conventional treatment with additional supplementation with raw rhubarb extract (rhubarb group) (Fig. 1). The patients provided written informed consent prior to their participation in the present study. Patients with stage IV acute gastrointestinal injury were not suitable for enteral nutrition and were therefore excluded from the present trial (11). The baseline clinical data of the patients are presented in Table I.

Treatment. All patients with heat stroke underwent conventional treatment, including lowering the core body temperature as close to normal as possible using cooling blankets, fluid infusion supplementation to maintain normal liquid and electrolyte levels as well as nutritional supplementation. Patients with multiple organ dysfunction syndrome (MODS) received organ function support, mechanical ventilation for respiratory failure and hemodialysis for severe renal failure. Patients in the rhubarb group received, in addition to conventional heat stroke treatment, a dose of Chinese rhubarb powder (Yalan Pharmaceutical Co., Ltd., Lanzhou, China; 0.3 g/kg body weight, soaked in 100 ml water at 80-100˚C for 30 min and then cooled to 37˚C) orally or via nasogastric tube once daily for five days. A previous study has demonstrated that the dose and powder suspension of rhubarb used in the present study has treatment efficacy (8).

Patient evaluation and biochemical analysis. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score (12) were recorded to estimate the disease severity in each patient. Venous blood samples were collected to measure the serum levels of interleukin (IL)-6 (cat. no. ab178013), C-reactive protein (CRP; cat. no. ab100630) and procalcitonin (PCT; cat. no. ab99995) using ELISA kits (Abcam, Cambridge, MA, USA). The white blood cell (WBC) count and the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also determined.

Endpoints. The primary endpoints of the present study were the length of stay (LOS) at the ICU, the LOS at the hospital and the 30-day mortality rate.

Statistical analysis. Categorical data are expressed as numbers and percentages, while quantitative data are expressed as the mean ± standard deviation, as appropriate. Comparisons of continuous variables were performed using the Mann-Whitney U- test. Comparisons of categorical variables were performed using the χ^2 test. Kaplan-Meier actuarial survival curves were calculated and the 30-day mortality was compared using the log-rank (Mantel-Cox) test. All statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 5 (GraphPad Inc., La Jolla, CA, USA). P<0.05 (two-sided) was considered to indicate a statistically significant difference.

Results

Rhubarb inhibits the expression of inflammatory factors. After the treatment, on days 3, 5 and 7 following admission, the WBC count, CRP, PCT and IL-6 levels had declined in each of the two groups. The WBC count in the group that received rhubarb supplementation was reduced compared with the conventional group on days 3 and 5 (12.93±2.49 vs. 16.10±4.57; P=0.003, 95% CI, 1.58-4.76 and 10.91±1.58 vs. 13.60±3.12; P=0.034, 95% CI, 1.62-3.77, respectively; Fig. 2A). Furthermore, the CRP levels in the rhubarb group were reduced compared with the conventional treatment group on days 3 and 5 (74.76±22.93 vs. 87.82±25.66; P=0.015, 95% CI, 2.55-23.57 and 39.18±17.00 vs. 51.98±18.97; P=0.002, 95% CI, 5.02-20.58, respectively; Fig. 2B). On treatment days 3, 5 and 7 the levels of PCT in the rhubarb group were reduced compared with the conventional treatment group, however there were no statistically significant differences between the two groups (Fig. 2C). The level of IL-6 in the rhubarb treatment group was lower than in the conventional treatment group on days 3, 5 and 7 (76.14±22.83 vs. 90.81±36.15; P=0.028, 95% CI, 1.59-27.75; 63.64±17.66 vs. 74.88±22.62; P=0.013, 95% CI, 2.47-20.01 and 45.43±12.26 vs. 61.47±17.71; P<0.001, 95% CI, 9.45-22.62; respectively; Fig. 2D).

Rhubarb improves liver and kidney function indices. The plasma levels of ALT in the rhubarb group were significantly lower than those in the conventional group on day 5 (82.50±17.57 vs. 93.24±16.72; P=0.005; 95% CI, 3.35-18.14; Fig. 3A) and day 7 (43.43±10.47 vs. 50.57±13.43; P=0.008; 95% CI, 1.89-12.38). The AST levels in the rhubarb group on days 3, 5 and 7 were reduced compared with the conventional group (145.73±25.60 vs. 159.23±22.79; P=0.012, 95% CI, 3.05-23.96; 99.87±28.38 vs. 114.03±28.86; P=0.025, 95% CI, 1.81-26.51; and 54.95±17.32 vs. 67.69 ±20.46; P=0.003, 95% CI, 4.55-20.92, respectively; Fig. 3B). There was no significant difference in the levels of blood urea nitrogen between the two groups throughout the observation period (P>0.05; Fig. 3C). Serum creatinine levels in the rhubarb group were lower than in the conventional treatment group on day 3 (156.78±30.87 vs. 178.73±36.81; P=0.004; 95% CI, 7.28-36.62), day 5 (114.23±23.25 vs. 128.25±28.05; P=0.014; 95% CI, 2.89-25.14) and day 7 (81.74±15.69 vs. 95.33±20.65; P=0.001; 95% CI, 5.67-21.52; Fig. 3D).

Rhubarb decreases the disease severity score and shortens length of ICU and hospital stay. The APACHE II scores of patients in the rhubarb group on treatment days 5 and 7 were reduced compared with the conventional group (20.10±2.28 vs. 22.28±2.88, P<0.001; 95% CI, 1.06-3.31 and 15.36±2.95 vs. 18.30±5.08, P=0.002; 95% CI, 1.15-4.74, respectively; Fig. 4A). Rhubarb treatment combined with conventional treatment significantly reduced the length of ICU stay (9.60±1.86 vs. 11.77±3.05; P<0.001; 95% CI, 1.08-3.26) and hospital stay (16.17±3.57 vs. 20.40±6.34; P<0.001; 95% CI, 2.00-6.45; Fig. 4B).

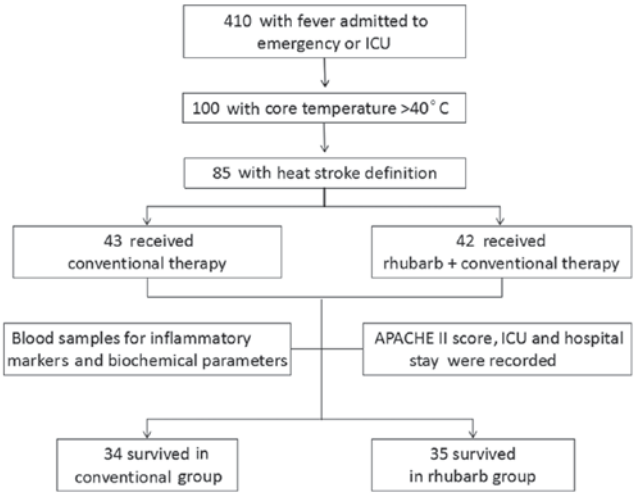

Figure 1. Scheme depicting the flow of the patients through the study. ICU, intensive care unit.

30-day mortality. Within the study cohort, 9 mortalities occurred in the conventional therapy group and 7 in the rhubarb group. Analysis of the survival curves revealed no significant difference in 30-day mortality between the 2 treatment groups (χ^2=0.1229; P=0.7260; Fig. 4C).

Adverse events. The records of nausea and vomiting caused by heat stroke prior to taking rhubarb were excluded. The new adverse effects following the administration of rhubarb included mild nausea (7/42 cases; 16.6%), vomiting (4/42 cases; 9.5%) and mild abdominal pain (15/42 cases; 35.7%), while no severe diarrhea was observed. These adverse effects did not affect the patients' vital signs. No specific treatment was administered to eliminate these adverse symptoms.

Discussion

The major results of the present are that rhubarb administration leads to downregulation of the systemic pro-inflammatory mediators in heat stroke patients. Rhubarb facilitates the healing of heat stroke-associated acute liver and kidney injury.

Heat stroke may cause abnormal function in multiple organs. The major cause for MODS is an uncontrolled thermoregulatory response to exercise after an episode of exertional heat stroke (13). Dysfunction of the intestinal barrier may be caused by heat stroke and may lead to increased intestinal permeability (14). High-intensity exercise-induced hyperthermia leading to a core temperature of >39˚C directly increases intestinal permeability, allowing endotoxins of Gram-positive and Gram-negative bacteria to translocate through the intestinal barrier and reach the blood stream. These endotoxins are recognized by the immune system and trigger a systemic inflammatory response (15-18). Protection of intestinal permeability and reduction of inflammatory factors is a problem for dogs with heat stroke, though continuous hemofiltration rapidly lowers the body the temperature, normalizes hemodynamics and electrolytes, improves serum enzyme concentrations and enhances the probability of survival (19). The reduction of inflammatory cytokine IL-6 and elevation of anti-inflammatory cytokine IL-10 secretion and improvement of hepatic, renal and lung dysfunction have been demonstrated in the treatment of thermoplegia (20). Taking these results into account, targeting of inflammatory cytokines has been proposed as a therapeutic goal to prevent MODS in heat stroke (20).

A previous study by our group indicated that administration of rhubarb to critically ill patients with MODS improved clinical outcomes. Protection of the intestinal barrier by rhubarb components may inhibit the inflammatory response and improve organ function in heat stroke patients (14). Previous studies demonstrated that rhubarb significantly improves gastrointestinal function, limits disease severity and mitigates the disease-associated damage to liver and kidney function in patients with severe acute pancreatitis (9). Rhubarb also reduced the inflammatory response and restored intestinal function in patients with severe acute pancreatitis or intra-abdominal hypertension, and rhubarb extract partially improved mucosal integrity in chemotherapy-induced intestinal mucositis (9,21,22).

Emodin, one of the active components of rhubarb, activates the Janus kinase (JAK)1/signal transducer and activator of transcription (STAT)3 signaling pathway to protect the jejunum in sepsis patients (10). Emodin was also reported to inhibit oxidative stress and inflammatory response to lung injury via the p38 mitogen-activated protein kinase pathway during sepsis and significantly alleviate sodium taurocholate-induced pancreatic acinar cell injury by decreasing the release of inflammatory factors (tumor necrosis factor-α, IL-1β and IL-6) (23,24). The active components of rhubarb may have an important role in heat stroke by modulating molecular signaling pathways including junction proteins (25) and JAK1/STAT3 (10). Although experimental studies claim that rhubarb and rhein have a protective effect on rats with brain damage (26,27), such a phenomenon occurring in the brains of the patients of the present study was not observable to judge the improvement of the state of mind of patients linked to the application of rhubarb.

The present results have valuable clinical implications. Although exogenous hypothermia treatment may reduce the core temperature of affected patients, cooling therapy does not repair intestinal barrier injury, a response closely linked to inflammatory response control. First, the result that rhubarb supports organ repair provides a novel anti-inflammatory therapy for heat stroke patients once a diagnosis of MODS has been established. Furthermore, rhubarb supplementation represents a novel therapeutic strategy for improved patient recovery following heat stroke.

The present study was limited by a relatively small sample size and studies on the dosing of rhubarb remain to be completed. These factors may limit the impact of the present results. Further randomized, multicenter studies are now required to clarify this important issue. A multicenter observational study will be performed in the future to elucidate the pharmacological parameters and physiological mechanisms of additive rhubarb therapy for heat stroke. The lack of long-term patient follow-up was another limitation of the present study. The purpose of the present study was to observe the anti-inflammatory effects of rhubarb on heat stroke, and the design did not include any long-term follow-up plan, which will, however, be included in future studies.

Table I. Demographics and clinical characteristics on admission.

Characteristic	Conventional group (n=43)	Rhubarb group (n=42)	P-value
Male/female	33/10	28/14	0.345
Age, years (mean ± SD)	50.2±17.2	53.8±19.4	0.368
Cause of heat stroke (%)			
Prolonged sun exposure outdoors	35 (81.4)	32 (76.1)	0.064
Prolonged exposure to high temperatures and humidity indoors	8 (18.6)	10 (23.8)	
Underlying diseases (%)			
Hypertension	7 (16.3)	9 (21.4)	0.544
Diabetes	4 (9.3)	6 (14.3)	0.354
Subacute thyroiditis	0 (0)	1 (2.4)	0.494
Hyperthyroidism	2 (4.7)	1 (2.4)	1.000
Chronic obstructive pulmonary disease	6 (14.0)	8 (19.0)	0.571
None	24 (55.8)	17 (40.5)	0.195

SD, standard deviation.

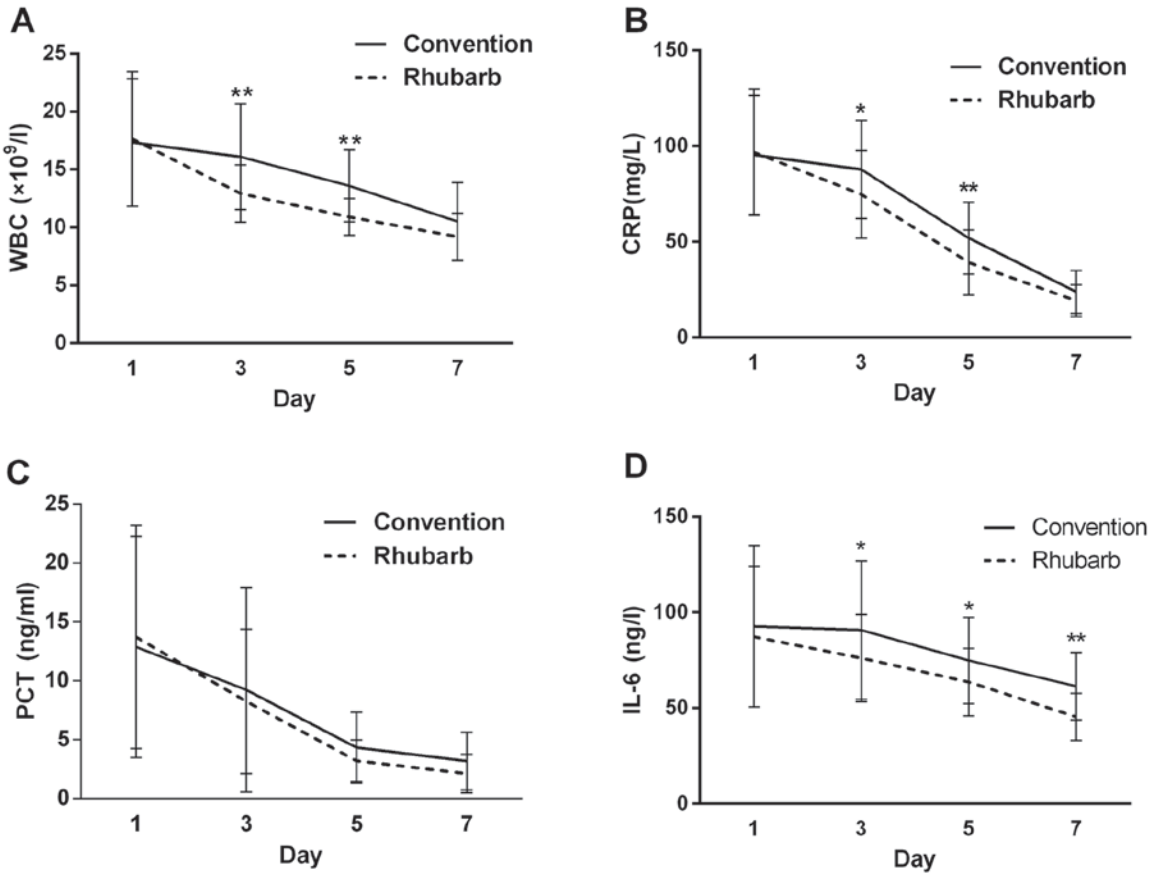

Figure 2. Laboratory values in the two groups over the course of the study. (A) WBC, (B) CRP, (C) PCT and (D) IL-6 levels in the two groups. The WBC count in the group that received rhubarb supplementation was reduced compared with the conventional group on days 3 and 5. The CRP levels in the rhubarb group were reduced compared with the conventional group on days 3 and 5. There were no significant differences observed in the levels of PCT between the two groups throughout the observation period. The level of IL-6 in the rhubarb group was reduced compared with the conventional group on days 3, 5 and 7. *P<0.05; **P<0.01, rhubarb group vs. conventional group. WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6.

In conclusion, the present study demonstrated that rhubarb supplementation protects organ function and inhibits inflammation in patients suffering from heat stroke. These results suggest that rhubarb supplementation may serve as a beneficial additive clinical treatment for heat stroke patients.

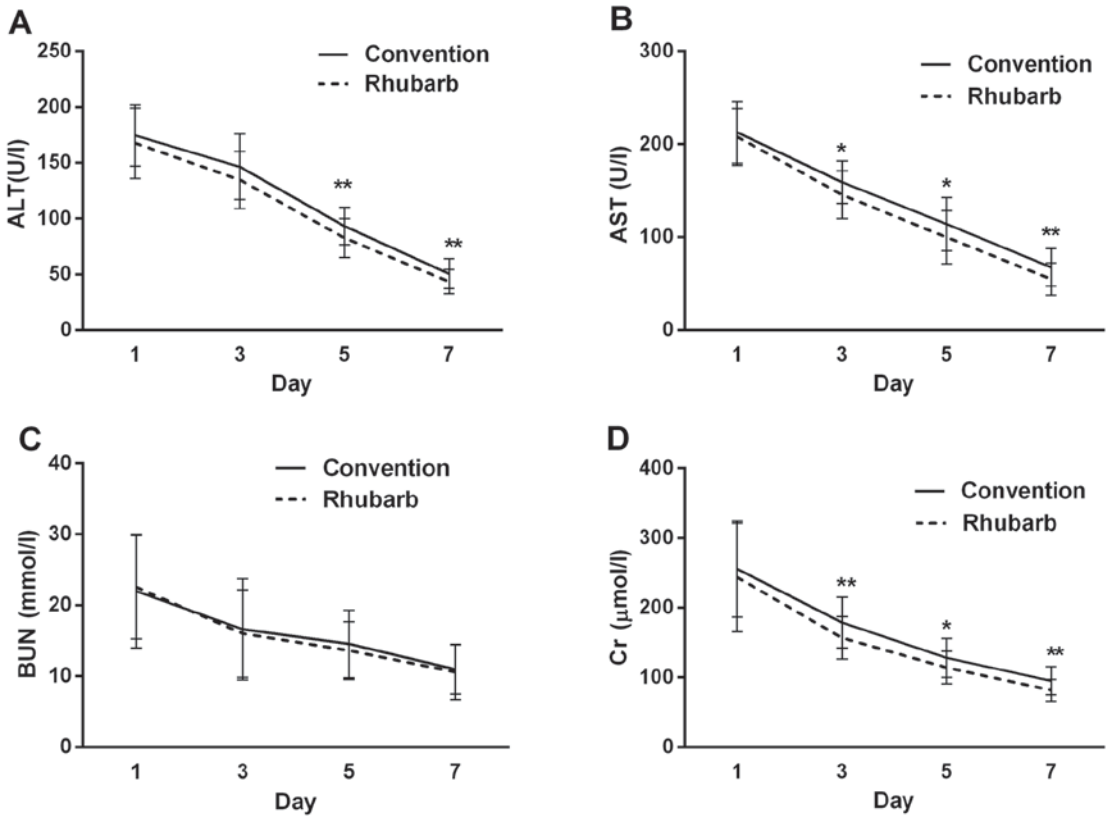

Figure 3. Liver and kidney parameters in the two groups over the course of the study. (A) ALT, (B) AST, (C) BUN and (D) Cr. The plasma levels of ALT in the rhubarb group were reduced compared with the conventional group on days 5 and 7. The plasma levels of AST in the rhubarb group were lower than in the conventional group on days 3, 5 and 7. There was no significant difference in the levels of BUN between the two groups. The levels of serum Cr in the rhubarb group were lower than in the conventional group on days 3, 5 and 7. *P<0.05; **P<0.01, rhubarb group vs. conventional group. Cr, creatinine; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

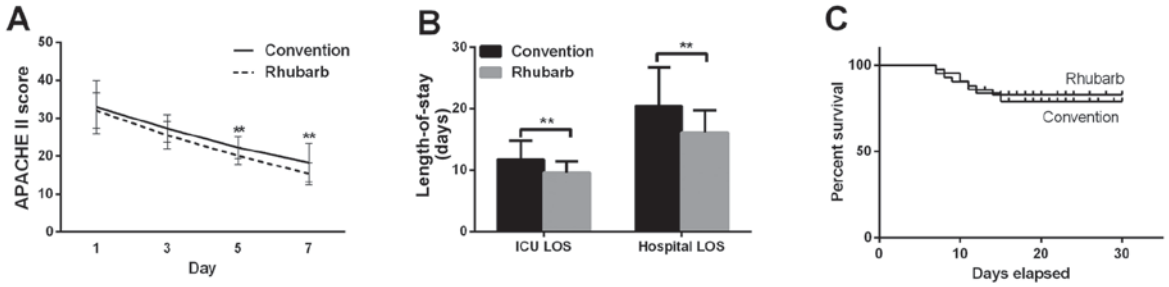

Figure 4. (A) APACHE II score, (B) LOS and (C) 30-day survival of patients in the two groups. The APACHE II score in the rhubarb group was significantly lower than that in the conventional group on days 5 and 7. Rhubarb treatment reduced the LOS at the ICU and at the hospital. The survival curves indicated no significant difference in 30-day mortality. **P<0.01 rhubarb group vs. conventional group. ICU, intensive care unit; LOS, length of stay; APACHE, Acute Physiology and Chronic Health Evaluation.

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Availability of data and materials

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

Authors' contributions

BW designed the study. YW, S-SS, H-YF, Y-KX and QL performed the experiments. YW, J-TY and BW analyzed the data. S-SS and YW prepared the figures and drafted the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Jiangsu University (Jiangsu, China). All patients provided written informed consent prior to their inclusion within the study.

Patient consent for publication

All patients involved in the study provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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