Saikosaponin a attenuates hyperlipidemic pancreatitis in rats via the PPAR-γ/NF-κB signaling pathway

PINGPING FENG¹, YANFANG XU¹, BAOYAN TONG¹, XIAOQUN TONG¹, YINYAN BIAN¹, SHUFEN ZHAO¹ and HONGBO SHEN²

¹Department of Digestion, Lin’an District Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang 311300; ²Department of Hepatobiliary Surgery, Quzhou People’s Hospital, Quzhou, Zhejiang 324000, P.R. China

Received March 20, 2019; Accepted November 5, 2019

DOI: 10.3892/etm.2019.8324

Abstract. The therapeutic effect of saikosaponin a (SSa) on hyperlipidemic pancreatitis (HP) is not completely understood. The aim of the present study was to investigate the therapeutic effect and the underlying mechanism of SSa using a rat model of HP. Following successful establishment of the HP rat model, different doses of SSa (low dose group, 10 mg/kg or high dose group, 20 mg/kg) were administrated. Histopathological examination, the wet/dry (W/D) ratio and myeloperoxidase (MPO) activity of the pancreatic tissues were assessed. The lipid, amylase (AMY), lipase and proinflammatory cytokine profiles in serum, as well as the expression of peroxisome proliferator-activated receptor (PPAR)-γ and the NF-κB signaling pathway-related proteins in pancreatic tissues were evaluated. The results showed that SSa effectively attenuated pancreatic pathological injury and reduced both the W/D ratio and MPO activity compared to the HP model rats. SSa also improved lipid metabolism by significantly decreasing the serum levels of total cholesterol and triglycerides (P<0.05). Following the administration of SSa, the activity of AMY and lipase, as well as the levels of the proinflammatory cytokines tumor necrosis factor-α, interleukin (IL)-1β and IL-6 were reduced, particularly in the high dosage group (P<0.05). Furthermore, SSa activated PPAR-γ expression and suppressed the NF-κB signaling pathway in pancreatic tissues. The present study suggested that SSa attenuated HP in rats by increasing lipid metabolism and inhibiting the release of proinflammatory cytokines via the NF-κB inflammatory pathway. The results from the present study indicated that SSa might be a promising therapeutic agent for the treatment of HP.

Introduction

Acute pancreatitis (AP) is one of the most common causes of hospital admissions worldwide and the incidence continues to rise annually (1). Although the majority of patients present with mild AP, which can be promptly diagnosed and cured, a notable number of patients go on to develop severe AP, causing systemic inflammatory responses, multiple-organ failure and even death (2). Despite improvements in the diagnosis and treatment of AP, the mortality rate of the disease remains ~5% (3). Gallstones and alcohol abuse represent the first and second most frequent causes of AP, respectively. However, hyperlipidemia is also a rare but important etiology of AP (4-6). The typical presentation of hyperlipidemic pancreatitis (HP) is a patient with a pre-existing abnormal lipid profile (7). A serum triglyceride (TG) level ≥1,000 mg/dl has been reported to precipitate an episode of AP (7). Inflammation and abnormal lipid metabolism are primary contributors to the pathogenesis of HP (8). A rapid reduction in serum TG levels can effectively prevent further worsening of a patient’s condition and the routine management of HP is often similar to that of AP caused by other factors (9). Multiple treatment strategies have been used for the management of patients with HP (10). The therapeutic mechanisms are largely based on a combination of the inflammatory response, abnormal lipid metabolism, extensive accumulation of free fatty acids and microcirculatory disturbance (2,11,12).

The saikosaponins (SSs), including saikosaponin a (SSa; Fig. 1), are the most active ingredients isolated from Radix Bupleuri, which is used in traditional Chinese medicine (13). This herb has long been utilized for inflammatory diseases, chronic hepatitis, influenza and digestive ulcers (14). Emerging evidence has suggested that SSs display anti-inflammatory, antiviral, antioxidant, antitumor, immune regulatory and central nervous system protective effects (13,15). Among the SSs, SSa has attracted considerable attention due to its significant anti-inflammatory activity (16). Direct inhibition of proinflammatory cytokine expression and regulation of the inflammatory response via specific signaling pathways, such as the NF-κB signaling pathway, have been identified as critical mechanisms underlying the anti-inflammatory activity of SSa (17). Additionally, previous studies have confirmed that SSa can regulate lipid metabolism and promote cholesterol...
efflux in early atherosclerosis, SSa may also serve as a potential peroxisome proliferator-activated receptor (PPAR)-γ agonist, significantly boosting the expression of PPAR-γ (18). PPARs usually interact closely with NF-κB, suppressing its signaling pathway and subsequently inhibiting the release of proinflammatory cytokines (19). Furthermore, PPAR agonists have been demonstrated to serve a pivotal role in controlling lipid metabolism and are capable of inhibiting AP-associated inflammatory responses (20,21). However, the effect of SSa on HP and the underlying mechanisms remain unclear.

The current study aimed to investigate the therapeutic effect and underlying mechanisms of SSa in rats with HP. A rat model of hyperlipidemia-induced pancreatitis was employed to assess lipid and proinflammatory cytokine profiles, as well as the expression of PPAR-γ and NF-κB.

Materials and methods

Reagents. SSa was purchased from Beijing Baiaolaibo Technology Co., Ltd. The assay kits for total cholesterol (TC, cat. no. A111-1-1), TG (cat. no. A110-1-1), low-density lipoprotein-cholesterol (LDL-C; cat. no. A113-1-1), high-density lipoprotein cholesterol (HDL-C; cat. no. A112-1-1), myeloperoxidase (MPO; cat. no. A044-1-1), amylase (AMY; cat. no. C016-1-1) and lipase (cat. no. A054-1-1) were purchased from Nanjing Jiancheng Bioengineering Institute. ELISA kits for rat tumor necrosis factor (TNF)-α (cat. no. MM-0180R1), interleukin (IL)-1β (cat. no. MM-0047R1), IL-6 (cat. no. MM-9106702) and IL-10 (cat. no. MM-0195R1) were obtained from Zhongsheng Beikong Bio-Technology. Additionally, rabbit anti-rat PPAR-γ antibody (cat. no. ab59256), rabbit anti-rat NF-κB antibody (cat. no. ab32536), rabbit anti-rat phosphorylated-(p)-NF-κB antibody (cat. no. ab86299), rabbit anti-rat inhibitor of κ-Bα (cat. no. Iκ-Bα) antibody (cat. no. ab32518), rabbit anti-rat p-Iκ-Bα antibody (cat. no. ab92700) and rabbit anti-rat myeloid differentiation primary response protein (Myd88) antibody (cat. no. ab2064) were purchased from Abcam.

Animals. 50 Male Sprague-Dawley (SD) rats (8 weeks of age, 200-230 g) were purchased from the Centre of Experimental Animals at the Nanjing Medical University. All the animal experiments were performed in collaboration with Zhejiang Traditional Chinese Medicine University and were approved by the Ethics Committee of Zhejiang Traditional Chinese Medicine University. Additionally, all animals received humane care according to the criteria outlined in the ‘Guide for the Care and Use of Laboratory Animals’ prepared by the National Academy of Sciences and published by the National Institutes of Health (22). The animals were housed at 20±2˚C, 55±10% humidity, with 12-h light/dark cycles and free access to water and food and were allowed to acclimatize for one week prior to experimentation.

Model preparation and animal grouping. SD rats were randomly divided into two groups. A group of 10 rats receiving a normal diet were regarded as the control group (n=10). 40 hyperlipidemic animal models were established according to previous publications (23,24) and received a high-fat diet for two weeks to induce hyperlipidemia. Serum lipid levels, including TC and TG, were also measured and met the hyperlipidemic criteria (23). The acute pancreatitis model was then further induced according to the methods described by Niyaz et al (25) and Shi et al (26). After a 12-h fast, the hyperlipidemic rats were anesthetized by the intraperitoneal injection of pentobarbital sodium (30 mg/kg). An abdominal midline incision was made and the rat’s abdominal cavity was exposed. Subsequently, rats received a retrograde infusion of 5% sodium taurocholate (0.1 ml/100 g; Sigma-Adrlich; Merck KGaA) into the bile-pancreatic duct to create the AP model. The biliopancreatic duct that enters the duodenum was clipped using a vascular clip for 5 min to prevent the solution from entering the bile duct, allowing the induction of the HP model. The control group (sham operation) was subjected to the same procedure; however, the sodium taurocholate was replaced with an equal volume of saline (0.1 ml/100 g). During the operation and the following 12 h, there was a mortality rate of ~23% in acute pancreatitis animals. The remaining HP rats were then randomly assigned into three groups (n=10 in each group): Model group, low SSa group (LSSa, 10 mg/kg) and high SSa (HSSa, 20 mg/kg). The animal grouping strategy used in the current study was similar to a previous study (26). The dose of SSa administrated in the current study was determined according to a previous publication (16). SSa was administrated by intraperitoneal injection 1 h before inducing HP. The same volume of normal saline was injected into the control and model group. All rats were anesthetized with 30 mg/kg pentobarbital sodium, 12 h after surgery. Blood samples were collected via cardiac puncture and centrifuged at 900 x g for 10 min to obtain the serum sample which was stored at -80˚C for subsequent analysis. The pancreatic tissues were immediately removed, snap frozen in liquid nitrogen and stored at -80˚C for subsequent analysis.

Histopathological examination. Pancreatic tissues from each group were fixed in 4% paraformaldehyde for 12 h at room temperature and embedded in paraffin. The tissues sections (4 µm thick) were stained with hematoxylin and eosin (H&E) for 5 min and 1 min, respectively, at room temperature and then observed under a light microscope (x400 magnification) for histopathological examination. The degree of pancreatic injury was histologically scored according to the standard scale described by Schmidt et al (27), including the graded assessment of pancreatic edema, inflammatory cell infiltration and acinar necrosis in pancreatic tissues.

Pancreas wet/dry (W/D) ratio. After the rats were sacrificed, freshly collected pancreatic tissues were weighed in the wet state. The pancreatic tissues were then dried at 80˚C for 48 h and the final dry weight was obtained. The W/D ratio was used to assess the edema of the pancreas.

MPO assay. The activity of MPO, an inflammatory marker associated with neutrophil infiltration (28), was measured in the pancreatic tissues with three replicates using the aforementioned test kit according to the manufacturer’s instructions.

Measurement of lipid profile, AMY and lipase activity in the serum. Blood biochemical parameters of the lipid profile were assessed. The concentrations of TC, TG, LDL-C and HDL-C
in rat serum were measured using the aforementioned assay kits according to manufacturer's instructions with an automatic biochemistry analyzer (Uni Cel Dx C 800Synchron; Beckman Coulter, Inc.) in triplicate. The AMY and lipase concentration in serum were also measured according to manufacturer's instructions in triplicates.

ELISA. Serum levels of inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-10 were determined using an ELISA with three replicates. The assays were performed in triplicate using the corresponding ELISA kits and a microplate reader according to the manufacturer's instructions.

Western blot assay. Pancreatic tissues from each group were obtained immediately after the rats were sacrificed. Total protein was extracted using RIPA lysis buffer (Beyotime Institute of Biotechnology) from the pancreatic tissues and the protein concentrations were measured using a bicinchoninic acid assay kit. Subsequently, equal amounts of each protein sample (100 µg) were separated via SDS-PAGE on 10% gels and transferred onto nitrocellulose filter membranes. After blocking with 5% non-fat milk at room temperature for 1 h, the membranes were incubated at 4˚C overnight with primary antibodies against PPAR-α, MyD88 (1:1,000), p-NF-κB (1:5,000), p-IL-6 and p-IL-10, NF-κB (1:5,000) and β-actin (cat. no. ab205718; 1:5,000; Abcam) was used as an internal control to determine protein levels and each experiment were performed in triplicate.

Statistical analysis. All data are expressed as mean ± SD. Statistical analysis was performed using SPSS software (version 19.0; IBM Corp.). Statistical differences between the groups were determined using one-way ANOVA followed by the Bonferroni post hoc test. P<0.05 was considered to indicate a statistically significant difference.

Results

Histopathological analysis of pancreatic tissue. The pancreatic tissues from all the groups were collected and stained with H&E (Fig. 2A-D). Pancreatic tissue of control rats displayed a normal pathological score and showed clear tissue structure with no obvious abnormality in the pancreatic ducts and acini. Pancreatic tissue obtained from rats in the model group displayed interstitial edema, interstitial hyperemia, necrosis and neutrophil granulocyte infiltration. The pathological score was also significantly increased in the model group compared with the control group (P<0.01; Fig. 2E). However, an improvement in pathological changes was observed following SSa treatment at both doses and pathological scores were reduced compared with those of the model group (P<0.05; Fig. 2E).

Effects of SSa on the pancreas W/D ratio and MPO activity. The effect of SSa on pancreatic edema was represented by the W/D ratio. Compared with that of the control, the W/D ratio was significantly increased in the model group and was reduced following the administration of SSa in dose-dependent manner (P<0.05; Fig. 3A). For MPO activity, a significant increase in pancreatic MPO activity was observed in the model group compared with the control group (P<0.01; Fig. 3B) and SSa inhibited this HP-induced MPO activity, especially in the high dosage group (P<0.05).

Determination of serum TC, TG, LDL-C and HDL-C levels. The levels of serum TC, TG, LDL-C and HDL-C were assessed to evaluate the alterations in lipid profiles in different groups. As shown in Fig. 4, the serum concentration of TC, TG, LDL-C and HDL-C varied among the groups. In the model group, the TC, TG and LDL-C levels were significantly higher than those in the control group (P<0.01), which indicated that high lipid levels were associated with HP. The level of TC in the model group and SSa groups was significantly higher than that in the control group (P<0.01). The administration of SSa (LSSa and HSSa group) significantly decreased the level of TC compared with the model group, particularly in the HSSa group (P<0.01; Fig. 4A). Regarding TG levels in serum, a similar pattern was also observed. SSa treatment significantly reduced TG levels in the LSSa group compared with the control group (P<0.01). Furthermore, no statistically significant difference was observed between the control and HSSa groups, suggesting a pronounced effect of SSa in lowering TG levels (Fig. 4B). There was also no significant difference in serum LDL-C levels between the model group and LSSa group, but LDL-C levels in the HSSa group were significantly decreased compared with those in the model group (P<0.01; Fig. 4C). By contrast, the model group displayed lower HDL-C levels than the control group and SSa treatment increased the levels of HDL-C compared with those in the model group (Fig. 4D).

Serum levels of AMY and lipase activity. Serum levels of AMY and lipase activity were subsequently determined (Fig. 5A and B). Compared with the control group, the levels of AMY and lipase were significantly increased in the model group (both P<0.01). Following SSa treatment, significant differences were observed between the model group and SSa groups (P<0.05).

Serum levels of TNF-α, IL-1β, IL-6 and IL-10. The expression levels of inflammatory cytokines in the serum were measured by ELISA. The significantly higher levels of TNF-α, IL-1β and
IL-6 in the model group compared with those in the control group (P<0.01) suggested that HP may be associated with the overproduction of inflammatory cytokines and the inflammatory response (Fig. 6). However, the levels of TNF-α, IL-1β and IL-6 were reduced following the administration of SSa, especially in the HSSa group, although not to the levels of the untreated controls. The levels of TNF-α in the model group increased significantly, by ~3-fold, compared with those in the control group (P<0.01) and were significantly decreased in the LSSa and HSSa groups compared with those in the model group (P<0.05; Fig. 6A). Similar outcomes were also observed for the expression levels of IL-1β and IL-6, with slight differences among the experimental groups (Fig. 6B and C). The model group had the highest levels of these three cytokines, followed by the LSSa and HSSa groups. The control group displayed the lowest expression levels of these three cytokines. The expression levels of IL-10, an anti-inflammatory cytokine (29), in the model group were higher than those in the control group (P<0.01) and were increased following SSa treatment (Fig. 6D). When HP model rats were treated with SSa, the expression levels of IL-10 significantly increased in the HSSa group (P<0.05; Fig. 6D). The aforementioned results suggested that SSa might have a therapeutic effect against inflammation in HP.

SSa promoted the expression of PPAR-γ in pancreatic tissues. The expression of PPAR-γ in pancreatic tissue was determined by western blotting to investigate the role of PPAR-γ in HP, as well as the effect of SSa on PPAR-γ expression. The protein expression levels of PPAR-γ were significantly decreased in the model group compared with those in the control group (P<0.01; Fig. 7A and B), but enhanced by SSa at both the low and high dosage compared with those in the model group, especially in HSSa group with significant difference compared to model group (P<0.01). This indicated that the expression levels of PPAR-γ in pancreatic tissue were reduced by HP and furthermore, the administration of SSa effectively increased PPAR-γ expression, inferring that SSa may be regarded as an ideal PPAR-γ agonist.

SSa suppressed NF-κB signaling in pancreatic tissues. Following the determination of the therapeutic role of SSa in the inflammatory response, it was speculated that this may be regulated by transcription factors involved in inflammatory pathways. To investigate whether SSa served an anti-inflammatory role in HP via the NF-κB signaling pathway, the protein expression of NF-κB, IκBα and MyD88 were detected by western blot analysis (Fig. 8A). The results showed that in the model group, the levels of
p-NF-κB p65, p-Ικ-Βα and MyD88 were elevated compared with those in the control group (P<0.01) (Fig. 8B-D). Whereas, treatment with SSa limited this HP-enhanced expression of p-NF-κB p65, p-Ικ-Βα and MyD88 in both the LSSa and the HSSa group. The expression of p-NF-κB p65, p-Ικ-Βα were significantly inhibited in LSSa group (P<0.05), and the expression of p-NF-κB p65, p-Ικ-Βα and MyD88 in HSSa group were significant decreased compared to the model group (P<0.01) (Fig. 8B-D). These results suggested that SSa inhibited the activation of the NF-κB signaling pathway in pancreatic tissues, thus suppressing the inflammatory response and regulating the release of proinflammatory cytokines.

Discussion

Hyperlipidemia is often a triggering factor for AP and the incidence of AP may also be accompanied by lipid metabolic disorders (30). Except for the commonly associated indicators, such as high levels of AMY and lipase, patients diagnosed with typical HP predominantly present with a pre-existing abnormal lipid profile, with a serum TG level...
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Furthermore, a previous study reported an earlier age of onset, severe pathological grade and higher mortality rates in patients with HP, compared with those with AP from other causes (31). In the present study, high levels of TC, TG and LDL-C were observed in HP rat models and the administration of SSa effectively attenuated the abnormal lipid profile.

Despite the complicated pathogenesis of HP, HP ultimately results in the activation of local and systemic inflammatory responses, as well as overproduction of inflammatory mediators (32). Inflammatory cytokines such as TNF-α, IL-1, IL-6 and IL-8, as well as a number of other cytokines, have a vital role in the occurrence and development of HP (33). Furthermore, activation of TNF-α induces the uncontrolled release of inflammatory mediators, including IL-6 and IL-8 (34). In a study carried out by Pérez et al (35), the upregulation of TNF-α, IL-6 and IL-1β in abdominal tissue was observed following the induction of pancreatitis in Wistar rats.

It is well known that the NF-κB signaling pathway is implicated in the pathogenesis of numerous inflammatory diseases.
such as asthma, arthritis (36,37). It is also hypothesized that the pathway exerts detrimental effects by inducing the expression of proinflammatory cytokines and activating the transcription of downstream inflammatory genes like Ik-B, causing tissue damage and even organ failure (36,38). The activation of the NF-κB signaling pathway is frequently observed in pancreatitis (39). Upon activation, this pathway controls the expression of proinflammatory cytokines including TNF-α, IL-1β, IL-6 and monocyte chemoattractant protein-1, and the regulation of the NF-κB signaling pathway has been confirmed as a treatment for pancreatitis in various studies (40,41).

In vitro studies indicate that SSa strongly inhibits the expression of proinflammatory cytokines including TNF-α, IL-1β, IL-6 and monocyte chemoattractant protein-1, and the regulation of the NF-κB signaling pathway has been confirmed as a treatment for pancreatitis in various studies (40,41). In mice with lipopolysaccharide-induced acute lung injury, SSa exerted a critical anti-inflammatory effect by inhibiting the expression of TNF-α and IL-1β, suppressing the NF-κB and NLR family pyrin domain containing 3 (NLRP3) signaling pathways (27). The NLRP3 inflammasome serves an important role in the maturation of IL-1β and the initiation of inflammatory cascades (44). Another study also found that NLRP3 mitigated injury to the pancreas and lungs, the inflammatory response and neutrophil infiltration in NLRP3-/- SAP mice (45). Similar results were observed in a rat model of chronic constriction injury, where SSa inhibited the levels of TNF-α, IL-1β and IL-6 and reduced the elevated expression of MAPK and NF-κB in the spinal cord, thus attenuating neuropathic pain (46).

In the current study, following the administration of a hyperlipidemic diet and sodium taurocholate to SD rats, the expression levels of inflammatory and chemotactic cytokines TNF-α, IL-1β and IL-6 were significantly increased (P<0.01) and NF-κB signaling was activated. Also, SSa treatment significantly decreased the expression levels of TNF-α, IL-1β and IL-6 and increased that of IL-10 (P<0.05). The results indicated that SSa has the ability to inhibit the secretion of pro-inflammatory cytokines and promote the production of anti-inflammatory cytokines to attenuate inflammation. Furthermore, the NF-κB signaling pathway was also regulated by administration of SSa. These results suggested that SSa served a protective role in the inflammatory response by regulating the NF-κB signaling pathway and reducing the expression of proinflammatory cytokines. SSa may also promote the expression of anti-inflammatory cytokines, thus modulating the inflammatory response and attenuating organ injury.

Our study showed that the expression of PPAR-γ was inhibited in HP rats and following treatment with SSa, the expression of PPAR-γ was effectively restored. PPARs are...
lipid-sensing nuclear receptors that are involved in metabolic diseases, including obesity, type 2 diabetes and various cardiovascular diseases (47). A series of studies have demonstrated the importance of PPARs in regulating inflammatory pathways in AP, by closely interacting with transcription factors such as NF-κB (48,49). Moreover, the preservation of PPAR expression by its agonists usually modulates inflammation by suppressing the activity of NF-κB, increasing the expression of IκBα and thereby inhibiting their nuclear transcriptional activity and signaling pathways (25). Previous studies investigated PPARs in inflammatory diseases and also found that PPAR activation mediates the NF-κB pathway and associated factors such as IκBα, MyD88 and toll-like receptor (TLR) 4 (50,51). It was also revealed that TLR4 contributes to the inflammation and tissue damage in AP (52). The NF-κB signaling pathway can be activated or inhibited by a number of factors, such as PPARs and TNF-α (53). Meanwhile, the upregulation of NF-κB by TNF-α can induce the release of proinflammatory cytokines (54).

In present study, during the operation and the following 12 h, there was a mortality rate of ~23% in acute pancreatitis animals. Previous studies reported similar mortality rates. In studies by Turkyilmaz et al (55,56), the mortality rate at 24 h after the operation was 43.75% in the acute pancreatitis rats. In a study by Hughes et al (57), the overall survival rate of the acute pancreatitis rats was 40% at 72 h and survival curves showed that the mortality rate at 12 h was ~15%. In a study by Chen et al (58), the mortality rate was 55% at 48 h in the acute hemorrhagic pancreatitis rat group. The cause of mortality in rats may be due to multiple-organ injury and failure after the induction of the acute pancreatitis model. Furthermore, a limitation of the present study is that the effect of SSa in hyperlipidemia rats without AP was not included, therefore it will be considered in future research.

In conclusion, the effect and therapeutic mechanism of SSa on rats with HP were investigated in present study. The results illustrated that SSa effectively improved lipid metabolism and significantly decreased the levels of MPO, AMY and lipase, especially at a high dosage (Px0.01). Following the administration of SSa, the levels of proinflammatory cytokines TNF-α, IL-1β and IL-6 were reduced, particularly at the high dosage, and the level of IL-10 expression was increased. Furthermore, as a potential agonist of PPAR-γ, SSa activated the expression of PPAR-γ and also suppressed the NF-κB signaling pathway in pancreatic tissues. These results indicated that the administration of SSa attenuated HP in rats by ameliorating lipid metabolism and inhibiting the release of proinflammatory cytokines, via suppressing the NF-κB signaling pathway and promoting the expression of PPAR-γ. Collectively, these results suggested that SSa may be a promising agent for the treatment of HP.

Acknowledgements

Not applicable.

Funding

This work was supported by the Science and Technology of Traditional Chinese Medicine of Zhejiang (grant no. 2017ZA120); Science and Technology Development Plan of Lin’an (grant no. 201604) and the Guided Science and Technology Project of Quzhou (grant no. 2016091).

Availability of data and materials

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

Authors’ contributions

PF and YX conceived the study. BT and XT analyzed and interpreted the data. PF, YB, SZ and HS collected the data, searched the literature, drafted the manuscript and plotted the figures and tables. PF was a major contributor in writing the manuscript and YX critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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