Regional haemodynamic variables and perfusion index in the evaluation of sciatic nerve block: a prospective observational trial

Bo Lu, Jingyan Jiang, Xiaoyu Li, Qingge Chen, Jinling Qin, Yun Chen, Junping Chen, Qing Shen

ABSTRACT

Objective We determined whether regional haemodynamics and perfusion index (PI) could be reliable indicators of a successful sciatic nerve block (SNB).

Design Prospective observational trial.

Setting A tertiary teaching hospital in China from April 2020 to August 2020.

Participants We assessed 79 patients for eligibility to participate in this study. Nine patients were excluded for not meeting our inclusion criteria, and three patients were excluded due to missing measurements at all time points.

Interventions The patients underwent SNB. Pulsed-wave Doppler and PI measurements were performed.

Primary and secondary outcome measures The primary outcome measure was the diagnostic power of regional haemodynamic change and PI to predict successful SNB. The secondary outcome measure was the effect of SNB on the regional haemodynamics and PI in the lower extremity.

Results We assessed 79 patients in this study and 67 patients available for the final analysis. The SNB was successful in 59 patients and failed in eight patients. There were no significant differences in demographic characteristics between the patients with successful and failed SNB. Starting from 10 min after SNB, the peak systolic velocity (PSV), end-diastolic velocity, time-averaged maximum velocity and time-averaged mean velocity of the anterior tibial artery and posterior tibial artery of patients in the successful SNB group were significantly higher than those in the failed SNB group (p<0.05). The PSV percentage increase at 10 min after SNB has great potential to predict the block success. The area under the receiver operating characteristic curve (AUC) values were 0.893 (95% CI 0.7809 to 1.000) and 0.880 (95% CI 0.7901 to 0.9699). The corresponding cut-off values were 19.22 and 35.88, respectively. The PI increased during 5–45 min intervals in patients with successful SNB. The AUC for the PI percentage increases at 10 min after SNB was 0.853 (95% CI 0.7035 to 1.000), with a cut-off value of 93.09.

Conclusion The regional haemodynamic variables, PSV and PI in particular, can be used as alternative indicators for clinicians to evaluate the success of SNB objectively and early.

Trial registration number ChiCTR2000030772.

Strengths and limitations of this study

- The four parameters of regional haemodynamics were obtained and the optimal predictor was screened out.
- Another strength of this study was that regional haemodynamics of the anterior tibial artery and posterior tibial artery were measured simultaneously to increase the reliability of the results.
- A limitation of this study was that the observation time point was limited to 45 min after the sciatic nerve block.

INTRODUCTION

Effectiveness of peripheral nerve blocks is traditionally evaluated by assessment of sensory or motor function, a practice varies in operators and requires patient cooperation. This can be particularly challenging in elderly patients with neurodegenerative diseases, in children, and in those who have neuropsychiatric disorders, or when there is a language barrier. Therefore, non-invasive, objective measures are needed for an accurate determination of success. However, most of the studies evaluating objective metrics (such as perfusion index (PI)) on regional blocks were about brachial plexus block (BPB) rather than on sciatic nerve block (SNB). Due to blockade latency and varied success rates of 71% and 97%, there is a need to investigate novel SNB assessments.

Objective methods for block assessment mainly depend on evaluating the sympathetic block and consequent physiological changes, such as vasodilation and in blood flow changes and skin temperature. PI calculated as the ratio of pulsatile blood flow to the non-pulsatile blood, measured in the index finger was found predictive for a successful supraclavicular nerve block. Correlations between regional haemodynamic changes and block

Correspondence to Dr Qing Shen; nbeysq666@163.com
were investigated in axillary BP, but the conclusion is not applicable in SNB, because the upper and lower limb arteries varied in distances to the heart and maximum diastolic degrees when the sympathetic nerves were blocked. Therefore, in this study, we aimed to investigate the changes in regional haemodynamics obtained via ultrasonography and PI in patients undergoing SNB and determined whether these parameters were reliable indicators of a successful SNB.

METHODS
Patients
We included adult (20–60 years) patients, with an American Society of Anesthesiologists physical status I and II, who were scheduled for elective lower limb orthopaedic surgery under general anaesthesia combined with SNB (figure 1). Patients with peripheral vascular disease, diabetes mellitus, chronic analgesic therapy, α and/or β blocker intake, neurological deficit, wounds or injuries that preclude application of ultrasonic probe, and patients with known contraindications to regional anaesthetic technique, such as an allergy to local anaesthetics, coagulopathy or local infection, were excluded.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Sciatic nerve block
The patients were taken into the anaesthesia induction room, which was at a temperature of 24°C. Electrocardiography, heart rate (HR), non-invasive blood pressure (BP) and pulse oximetry (SpO₂) were monitored throughout the procedures. Measurements and SNB did not initiate until 20 min on patient arrival to ensure each patient got accustomed to the surroundings.

Patients were placed in the lateral decubitus position, with the operating side on top, hip and knee flexed. Ultrasound-guided SNB was performed using a popliteal approach. A high-frequency ultrasound probe (SonoSite X-port; SonoSite, Washington, USA) was placed in the popliteal fossa, close to the popliteal crease to identify the tibial and common peroneal nerves and then trace the convergence to the sciatic nerve. A 22-gauge, 100 mm needle was inserted in-plane from the lateral thigh to approach the sciatic nerve and 20 mL of 0.3% ropivacaine (AstraZeneca B.V., Zoetermeer, the Netherlands) were injected in the space between the paraneural sheath and the epineurium. The injection should be presented with a solution spreading around the sciatic nerve or between the tibial and common peroneal components. All the ultrasound-guided SNB were performed by the same anaesthesiologist (BL).

Measurements
We used a commercially available non-invasive SpO₂ monitoring system (Radical-7, Masimo, California, USA) to measure PI on the big toe of lower limbs. Measurements were performed with patients resting in the supine position.

Regional haemodynamic parameters were measured by pulsed-wave Doppler (PWD) ultrasound (M7 super, Mindray Medical International, China) with a 12–4 MHz linear array transducer. We defined the location of the anterior tibial artery (ATA) as 1 cm proximal to the extensor retinaculum (figure 2A). The location of the posterior tibial artery (PTA) was defined to be halfway between the posterior border of the medial malleolus and the Achilles tendon (figure 2B). Specific points were located with a skin marker to provide consistency with all measurements taken.

After the B-mode US image was optimised, the PWD US mode was activated, the volume gate was positioned at the centre of the arterial lumen, and the gate’s size was adjusted to include the entire lumen of the ATA or PTA. Next, the angle of insolation was adjusted and maintained at 60°. Once an optimal PWD spectral waveform was achieved, it was automatically traced, and arterial haemodynamic parameters were displayed. To minimise measurement mistakes, we evaluated five consecutive cardiac cycles. The parameters included peak systolic velocity (PSV), end-diastolic velocity (EDV), time-averaged maximum velocity (TMax) and time-averaged mean velocity (TMean). All the ultrasound scans and recordings were performed by the same anaesthesiologist (QS).

The basal haemodynamic, US and PI data were recorded before the SNB. The US and PI data, as well as pinprick sensory scores, were recorded at 5 min intervals over a 45 min period in both blocked and non-blocked limbs following the completion of local anaesthetics injection. At each time point, we obtained US and PI data before

![Figure 1: Study flow diagram. EDV, end-diastolic velocity; PI, perfusion index; PSV, peak systolic velocity; SNB, sciatic nerve block; T<sub>A</sub>mean, time-averaged mean velocity; T<sub>A</sub>max, time-averaged maximum velocity.](http://example.com/figure1.png)
Figure 2  Pulsed-wave Doppler (PWD) ultrasound of the anterior tibial artery (ATA) and posterior tibial artery (PTA) before and 10–45 min after sciatic nerve block (SNB). (A, B) Position of the ultrasonic probe.
conducting the pinprick sensory tests. We performed the pinprick sensory tests with a 24-gauge blunt needle on the skin innervated by the sciatic nerve and evaluated the findings using the Hollmen scale to (0) normal transmission using the pinprick test; (1) needle sensed less than the contralateral extremity; (2) feeling the needle as a blunt object; (3) loss of tactile sense. We also recorded the non-invasive BP and HR at each time point.

Patients with a score of at least two on the Hollmen scale at 45 min after the block were defined as a successful blockade. After that, whether the SNB was successful or not, patients were transferred to the operating room and received general anaesthesia.

The primary outcome measure of this study was the diagnostic power of regional haemodynamic change and PI to predict successful SNB. The secondary outcome measure of this study was the effect of SNB on the regional haemodynamic and PI in the lower extremity.

**Statistical analysis**

The sample size was calculated using MedCalc Software V.19 (MedCalc Software bvba, Ostend, Belgium) to detect the area under the receiver operating characteristic (AUROC) curve of 0.80, and with a null hypothesis of an AUROC curve of 0.5. The rate of block failure was estimated to be 10%, based on our previous pilot study. Thus, we calculated a minimum number of 57 patients (with at least seven failed blocks) for a study power of 80% and α error of 0.05.

Categorical data were presented as frequencies (percentage). Continuous data were presented as the mean (SD) or median (quartiles), as appropriate. Data were tested for normality using the Kolmogorov Smirnov test. Between-group comparisons of normally distributed data were analysed using the independent sample t-test. Categorical data were compared using the χ² test or Fisher’s exact test, as appropriate. We used the repeated-measures analysis of variance to analyse the differences in variables (regional haemodynamic parameters, PI, mean arterial pressure (MAP), HR) between successful and failed blocked limbs, followed by a Bonferroni post hoc analysis to correct for multiple comparisons. A p<0.05 was considered statistically significant. As a diagnostic test, ROC curves were constructed to determine the sensitivity, specificity and cut-off values of blood flow or PI changes to predict successful SNB. The optimal cut-off point was determined using ROC curves with the maximum Youden index (sensitivity +specificity−1). All statistical analyses were performed using Prism V.8.0 (GraphPad, San Diego, California, USA).

**RESULTS**

We assessed 79 patients for eligibility to participate in this study. Nine patients were excluded for not meeting our inclusion criteria, and three patients were excluded due to missing measurements at all time points. This resulted in data from 67 patients available for the final analysis.

The SNB was successful in 59 patients and failed in 8 patients (figure 1). The types of surgery performed were ankle arthroscopy, excision of a thecal cyst, hallux valgus corrections, internal fixation and plate removal. There were no significant differences in demographic characteristics between the patients with successful and failed SNB (table 1). There were also no significant differences in MAP or HR between patients with successful and failed SNB (p>0.05) (table 2). The pinprick test showed that the Hollmen scale of successful SNB patients reached two points (feeling the needle as a blunt object) at 20 min postblock (table 3).

From the morphology of the PWD spectrum waveform, we deduced that the triphasic waveform changes to a monophasic waveform following SNB (figure 2). This is because the negative flow in the early diastole changes to a positive flow and the diastolic flow increases.

There were no significant differences in regional haemodynamic values between patients with successful and failed SNB at baseline and 5 min after SNB block (p>0.05). The PSV, EDV, TAmx and TAMean of ATA and PTA increased between 5 and 45 min compared with the baseline value in patients with successful SNB (p<0.05) (figure 3). Furthermore, starting from 10 min after SNB, the PSV, EDV, TAmx and TAMean of ATA and PTA of patients in the group with a successful SNB were significantly higher than those in the failed SNB group (p<0.05) (figure 3). Therefore, the time point of 10 min was selected for the prediction of successful block.

We constructed ROC curves displaying the percentage increase (relative to baseline) of parameters at 10 min after SNB to predict a successful block (figure 4). Our data suggest that the PSV percentage increase of ATA and PTA at 10 min after SNB has great potential to predict the block success. The AUROC curves were 0.893 (95% CI 0.7809 to 1.000) and 0.880 (95% CI 0.7901 to 0.9699), respectively (table 4). The corresponding cut-off values were 19.22 and 35.88, respectively (table 4).

The baseline PI of the big toe was comparable between patients with successful and failed SNB (p>0.05). The PI increased between 5 and 45 min compared with the baseline value in patients with successful SNB (p<0.05) (figure 5). The PI was higher in patients with a successful SNB than in patients with a failed SNB, starting 10 min after SNB (p<0.05) (figure 5). The AUROC curve for the

### Table 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Successful SNB (n=59)</th>
<th>Failed SNB (n=8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.10±7.96</td>
<td>43.01±15.99</td>
<td>0.977</td>
</tr>
<tr>
<td>Sex (female, %)</td>
<td>24 (40.68)</td>
<td>3 (37.5)</td>
<td>0.340</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.5±9.55</td>
<td>165.3±10.53</td>
<td>0.619</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.83±7.69</td>
<td>63.25±7.24</td>
<td>0.372</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or as N (%). SNB, sciatic nerve block.
PI percentage increases at 10 min after SNB was 0.853 (95% CI 0.7035 to 1.000), with a cut-off value of 93.09 (table 4).

**DISCUSSION**

In this study, we observed that regional haemodynamic data and PI of the big toe are early, quantitative and reliable indicators of a successful sciatic block. PSV and PI changes provide the most effective and objective measurements for the evaluation of SNB. We showed that regional haemodynamic data of ATA and PTA and PI values significantly increased from baseline as early as 10 min after successful SNB.

Blood flow was triphasic in all patients evaluated using Doppler ultrasonography. This type of circulation with high peripheral vascular resistance is most common in the extremities. In this study, we observed that, after successful SNB, the early diastolic reflux disappeared and the conversion of the spectral wave from triphasic waveform to monophasic waveform. Although the blocking effect cannot be judged from the waveform’s change, the monophasic waveform can qualitatively indicate the appearance of the SNB blocking effect.

Regional haemodynamic parameters and PI significantly changed at 10 min after SNB, which was before the onset time of sensory and motor block. The AUROC of PSV (ATA and PTA) and PI values significantly increased from baseline as early as 10 min after successful SNB.

Wu et al found that laser speckle contrast imaging can accurately measure the blood flow index of the toe to predict successful block, but this technology requires additional equipment. In terms of practicality, with increasing access and a short learning curve, Doppler ultrasonography is considered easy for beginners to use in many hospitals in China. The PI is presented numerically and is easy to interpret without a requirement for specifically trained personnel. For a thorough investigation of the measurements, two arteries and four haemodynamic parameters were studied, each turned out with a varied cut-off value. Moreover, PSV stood out to be the most predictive. Thus in future practice, we assume each index (PSV of ATA or PTA) alone is sufficient to predict the success of SNB with the same reliability. In brief, PI or PSV before and 10 min after SNB were recorded to generate the percentage in value change. By referring to the corresponding cut-off value, we make a preliminary conclusion of SNB effectiveness.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Successful SNB</td>
<td>Failed SNB</td>
</tr>
<tr>
<td>0</td>
<td>83.98±14.34</td>
<td>86.22±8.97</td>
</tr>
<tr>
<td>5</td>
<td>87.16±13.48</td>
<td>86.32±8.66</td>
</tr>
<tr>
<td>10</td>
<td>83.19±12.13</td>
<td>86.34±9.42</td>
</tr>
<tr>
<td>15</td>
<td>85.59±11.37</td>
<td>84.72±8.36</td>
</tr>
<tr>
<td>20</td>
<td>87.47±12.36</td>
<td>85.19±10.33</td>
</tr>
<tr>
<td>25</td>
<td>87.11±11.39</td>
<td>85.26±7.85</td>
</tr>
<tr>
<td>30</td>
<td>87.31±11.74</td>
<td>86.24±9.05</td>
</tr>
<tr>
<td>35</td>
<td>86.81±11.41</td>
<td>84.28±7.95</td>
</tr>
<tr>
<td>40</td>
<td>83.42±12.41</td>
<td>86.34±8.06</td>
</tr>
<tr>
<td>45</td>
<td>88.39±11.17</td>
<td>87.64±11.18</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.
HR, heart rate; MAP, mean arterial pressure; SNB, sciatic nerve block.

<table>
<thead>
<tr>
<th>Hollmen scale of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Successful SNB (n=59)</td>
</tr>
<tr>
<td>Failed SNB (n=8)</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR).
SNB, sciatic nerve block.
Figure 3  Regional haemodynamic parameters of the anterior tibial artery (ATA) and posterior tibial artery (PTA) after the sciatic nerve block (SNB). (A, E) Peak systolic velocity (PSV); (B, F) end-diastolic velocity (EDV); (C, G): time-averaged mean velocity (TAmean); (D, H) time-averaged maximum velocity (TAmx). Values are represented as the mean±SD *P<0.05, **P<0.01, *P<0.001, compared with successful SNB. ∆P<0.05, & p<0.001 compared with the baseline value.
Li et al showed that the haemodynamic changes of the brachial artery could be observed 5 min after BPB, indicating that the sympathetic block is achieved earlier than the sensory and motor block, and the authors argued that could be explained by the smaller diameter of the sympathetic nerve fibre. In our study, we did not detect a significant difference in regional haemodynamics between the successful and failed SNB until 10 min after SNB. This might be because the sciatic nerve is far larger than the brachial plexus and is surrounded by a tough neurovascular sheath. Therefore, sympathetic nerve blocks are slower than the BPB.

The blood supply at the lower extremity was provided by the PTA, ATA and peroneal artery. In this study, we selected the ATA and the PTA to measure blood flow velocity because the anatomical location of these two vessels is relatively shallow and fixed, allowing for easy conduct of ultrasound long-axis scanning. In addition, previous studies have shown that the skin temperature of the big toe increases earliest and most significantly after epidural block and SNB and, therefore, we chose the big toe for PI measurement.

We found that the baseline values of the velocity of ATA and PTA were different, resulting in a difference in the percentage increase of blood flow velocity after SNB block, which led to variable cut-off values for predicting the success of SNB. Based on this study and previously reported data, there is considerable individual variation in baseline values of blood flow velocity and PI. Regarding early and reliable prediction of block outcome, the critical factor is not the actual value itself but the relative change after SNB. Therefore, we chose to work with the percent change (relative to baseline), rather than absolute values.

## Table 4

<table>
<thead>
<tr>
<th>Parameters</th>
<th>AUC</th>
<th>95% CI</th>
<th>P value</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATA</td>
<td>∆PSV</td>
<td>0.8925</td>
<td>0.7809 to 1.000</td>
<td>&lt;0.0001</td>
<td>&gt;19.22</td>
<td>86.67</td>
</tr>
<tr>
<td></td>
<td>∆EDV</td>
<td>0.7477</td>
<td>0.6154 to 0.8800</td>
<td>0.0094</td>
<td>&gt;48.65</td>
<td>75.00</td>
</tr>
<tr>
<td></td>
<td>∆TAmean</td>
<td>0.8267</td>
<td>0.7282 to 0.9251</td>
<td>0.0010</td>
<td>&gt;72.88</td>
<td>68.33</td>
</tr>
<tr>
<td></td>
<td>∆TAmax</td>
<td>0.8500</td>
<td>0.7626 to 0.9374</td>
<td>0.0004</td>
<td>&gt;82.12</td>
<td>70.49</td>
</tr>
<tr>
<td>PTA</td>
<td>∆PSV</td>
<td>0.8800</td>
<td>0.7901 to 0.9699</td>
<td>0.0001</td>
<td>&gt;35.88</td>
<td>68.33</td>
</tr>
<tr>
<td></td>
<td>∆EDV</td>
<td>0.7858</td>
<td>0.6591 to 0.9126</td>
<td>0.0040</td>
<td>&gt;49.76</td>
<td>81.67</td>
</tr>
<tr>
<td></td>
<td>∆TAmean</td>
<td>0.8045</td>
<td>0.7014 to 0.9077</td>
<td>0.0014</td>
<td>&gt;53.32</td>
<td>68.33</td>
</tr>
<tr>
<td></td>
<td>∆TAmax</td>
<td>0.8525</td>
<td>0.7579 to 0.9471</td>
<td>0.0004</td>
<td>&gt;45.94</td>
<td>76.67</td>
</tr>
<tr>
<td>PI</td>
<td>∆PI</td>
<td>0.8525</td>
<td>0.7035 to 1.000</td>
<td>0.0004</td>
<td>&gt;93.09</td>
<td>86.67</td>
</tr>
</tbody>
</table>

ATA, anterior tibial artery; AUC, area under the receiver operating characteristic curve; EDV, end-diastolic velocity; PI, perfusion Index; PSV, peak systolic velocity; PTA, posterior tibial artery; TAmax, time-average maximum velocity; TAmean, time averaged mean velocity; ∆, percentage changes.
the difference between the PI of the blocked limb and unblocked limb is significantly reduced following general anaesthesia. The PI of the blocked limb is initially significantly increased after BPB. This may be due to peripheral vascular dilatation caused by general anaesthesia, which covers the increase of PI caused by BPB. We stopped our observations in this study before the induction of general anaesthesia. Therefore, it remains unclear whether regional haemodynamics and PI can predict the success of block in patients receiving SNB after general anaesthesia.

The blood flow velocity of both ATA and PTA was significantly increased after the SNB. However, how the four branches of the sciatic nerve innervate the vasodilation of the ATA and PTA remains unclear. It is also unclear whether the ATA and PTA show varying degrees of blood flow velocity changes when there is partial SNB failure. Future research should explore the changes in blood flow velocity after individually blocking the four branches of the sciatic nerve.

Galvin et al have investigated the effects of successful SNB on peripheral PI. This study found that the positive predictive value of the peripheral PI was 94%, much higher than in this study. Possible reasons for this difference may be the two studies varied in blocking techniques (ultrasound guided vs neurostimulator guided), anaesthetic medicine used (ropivacaine vs mepivacaine), endpoints of pinprick sensory tests (45 min vs 30 min) and time points of ROC curve (10 min after SNB vs 12 min).

There are several limitations to our study. First, only healthy patients were selected, excluding patients with pre-existing peripheral vascular disease, as vascular diseases may alter the degree of vasodilatation and the relative increase in blood flow and PI values. More investigation needs to be done in those groups in the future. Second, further research is needed to test whether these indices at 10 min are predictive of successful vs failed delayed onset of SNB. Third, to not interfere with the surgery process, we limited the observation time point to 45 min after the SNB, which might have affected the reported rate of a successful block. Fourth, there was a concentration–effect relationship between the local anaesthetic concentration and arterial blood flow, even though in this study, we selected only 0.3% ropivacaine as a local anaesthetic. Fifth, this study’s findings may not be applicable when an intraneural injection technique or block site below the bifurcation of the sciatic nerve is used.

In conclusion, both PSV and PI can be used as alternatives for clinicians to evaluate the success of SNB objectively and early.

Acknowledgements We are thankful to our colleagues in the Department of Anesthesiology, HwaMei Hospital.

Contributors BL is responsible for the overall content as guarantor. BL, QS and JC contributed conception and design of the study; BL wrote the manuscript; JJ and XL organised the database; BL, XL, OC, YC and QS conducted the study, collect and analysed data. All authors contributed to manuscript revision, read and approved the submitted version.

Funding This work was supported by grants from the Medical Scientific Research Foundation of Zhejiang Province, China (Grant No. 2020KY261, 2021H038, 2022KY332) and Key Medical Discipline of Ningbo (No. 2022-B10).

Disclaimer We declare that the funders had no role in the protocol design and collection, analysis, interpretation of data, either writing of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This prospective observational study was conducted at the HwaMei Hospital, University of Chinese Academy of Science, and included patients visiting the clinic from April 2020 to August 2020. The study obtained the approval of the Ethics Committee of HwaMei Hospital, University of Chinese Academy of Science (PJ-NBEY-KY-2020-131-01) and was registered as a clinical trial (ChiCTR2000030772, principal investigator: Bo Lu, Date of registration: 2020/03/14). Written informed consent was obtained from all participants before enrolment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Bo Lu http://orcid.org/0000-0003-1815-6778
Qing Shen http://orcid.org/0000-0001-6016-5518

REFERENCES


