

Optimal concentration of the transversus abdominis plane block in enhanced recovery after surgery protocols for patients of advanced age undergoing laparoscopic rectal cancer surgery

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Abstract

Objective: The transversus abdominis plane (TAP) block ameliorates visual analogue scale scores and decreases morphine requirements, but its role remains unclear. Patients of advanced age are susceptible to local anesthetic intoxication. We aimed to identify an optimal concentration that can be used in enhanced recovery after surgery (ERAS) without compromising analgesic efficacy.

Methods: In total, 120 patients aged ≥ 65 years undergoing laparoscopic rectal cancer surgery received general anesthesia combined with a TAP block using 0.25% ropivacaine (Group A), 0.50% ropivacaine (Group B), or 0.75% ropivacaine (Group C) in a 40-mL volume. Group D only received general anesthesia. Epinephrine, plasma cortisol, interleukin-6, and tumor necrosis factor- α were measured at baseline, skin incision, celiac exploration, and tracheal extubation. The proportions of CD4⁺ and CD4⁺/CD8⁺ cells were measured at baseline and postoperative days 1 and 3.

Results: The TAP block relieved the stress response and accelerated intestinal functional recovery as shown by significant reductions in VAS scores and anesthetic requirements. However, there was no significant difference between Groups B and C.

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Conclusion: The TAP block plays an important role in ERAS in older patients undergoing laparoscopic rectal cancer surgery, and 0.5% ropivacaine is an optimal concentration that can reduce toxicity without undermining analgesia.

Keywords

Transversus abdominis plane block, optimal concentration, enhanced recovery pathway, older patients, rectal cancer, laparoscopic surgery

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Key points summary

Question: What role does the TAP block play in patients of advanced age undergoing laparoscopic rectal cancer surgery?

Findings: The TAP block can mitigate the stress response and facilitate intestinal functional recovery.

Meaning: The TAP block plays an important role in fast-track surgery, especially in patients of advanced age undergoing laparoscopic rectal cancer surgery.

Introduction

Rectal cancer is one of the most common cancers worldwide.¹ The incidence rate is increasing in patients of advanced age, especially in Africa and Asia.^{1,2} The increasingly aged population and the rising cost of health care make efficient use of resources a priority. Aged patients often have multiple diseases, making reduction of the hospital cost and length of stay important. Research has indicated that the practice of enhanced recovery pathways in laparoscopic rectal surgery can shorten the time of hospitalization and reduce the cost.³ The prognosis of cancer depends not only on the tumor stage and histopathologic type but also on the patient's immune function.^{4,5} Anesthetic drugs have immunosuppressive effects, especially opioids.⁶ Opioid

drugs are typically used to relieve pain but can lead to adverse effects such as respiratory depression, nausea, immobilization, prolonged ileus, and reduced immune function.⁷ A feasible method to reduce the dose of opioids and enhance recovery during the perioperative period is needed for patients of advanced age.

The transversus abdominis plane (TAP) block can block the lower intercostal, ilioinguinal, and iliohypogastric nerves by injection of a local anesthetic in the neurovascular plane between the internal oblique and transversus abdominis muscles.⁸ The TAP block can reduce pain scores and decrease opioid demands in multimodal analgesia after open abdominal surgery and hysterectomy.^{9,10} Research has shown that the TAP block can also enhance recovery after surgery.^{3,11}

The use of TAP block to reduce pain from abdominal incisions is a novel technique for postoperative pain control.¹² In addition, elderly patients with rectal cancer always have hypoproteinemia, making them sensitive to local anesthetic intoxication. The purpose of this study was to discuss how TAP block affected stress response and immune function. We aimed to search an optimal concentration of TAP blocks to a well-standardized and optimized enhanced recovery pathway in elderly patients undergoing laparoscopic rectal surgery.

Methods

The study was approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University (Fujian, China) (No. 2015 [150]). Written informed consent was obtained from all patients. Patients undergoing laparoscopic rectal cancer surgery were recruited for the study. The inclusion criteria were an age of ≥ 65 years, body mass index of 18 to 30 kg/m^2 , and American Society of Anesthesiologists physical status of 1 or 2. The patients were randomly divided into four groups: Group A (0.25% ropivacaine), Group B (0.50% ropivacaine), Group C (0.75% ropivacaine), and Group D (general anesthesia only). Group randomization was performed using cards placed in opaque, sealed envelopes by an independent person not involved in this research. Each patient in all four TAP groups was given a dose of 40 mL of local anesthetic (20 mL on each side). The exclusion criteria were immune system or endocrine dysfunction and pretreatment with opioids, nonsteroidal anti-inflammatory drugs, hormones, or other immunomodulatory substances.

Based on the fast-track surgery protocol, no premedication was given, and all patients were fasted for 2 hours to clear liquids and 6 hours to clear solids.¹³

General anesthesia was induced with a target-controlled infusion of propofol (AstraZeneca S.p.A., Macclesfield, UK) aiming at a plasma concentration 3.0 to $3.5 \mu\text{g/mL}$, a bolus infusion of remifentanyl at 1.5 to $3.0 \mu\text{g/kg}$ (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China), and a bolus infusion of rocuronium at 0.5 to 0.8 mg/kg (N.V. Organon, Oss, the Netherlands). All patients were administered a target-controlled infusion of propofol and intravenous remifentanyl ($0.2\text{--}0.3 \mu\text{g/kg/min}$). Anesthetic depth was controlled by maintaining the bispectral index at 40 to 60. TAP blocks were performed after intubation by

the same anesthetist following the method described by Tran et al.¹⁴ We used a SonoSite M-Turbo ultrasound machine (SonoSite Inc., Bothell, WA, USA) and a 150-mm Stimuplex needle (B. Braun Medical, Bethlehem, PA, USA) with an in-plane approach. The probe was positioned between the costal margin and the iliac crest. When the needle tip reached the layer between the transversus abdominis and internal oblique muscles, 20 mL of local anesthetic was injected on each side. The patients received different concentrations of ropivacaine (H20140763; AstraZeneca AB, Sodertalje, Sweden) diluted with 0.9% saline to a total volume of 40 mL (20 mL on each side).

Every patient was given a patient-controlled intravenous analgesia pump (0.5 mg/mL of morphine, bolus of 2 mL, background infusion at 2 mL/h, lockout time of 15 min) for 24 hours. We removed the pump on postoperative day (POD) 1 and used intravenous morphine (1–2 mg) as a rescue analgesic if the patient's pain was >3 on the visual analogue scale (VAS) (0, no pain; 10, worst imaginable pain). Pain intensity was assessed by the VAS after tracheal extubation, on POD1, and on POD3. The time to first flatus, length of stay, and complications during the perioperative period were recorded.

The plasma levels of epinephrine (E), cortisol (Cor), interleukin (IL)-6, and tumor necrosis factor- α (TNF- α) were measured at baseline (t0), skin incision (t1), celiac exploration (t2), and tracheal extubation (t3) by enzyme-linked immunosorbent assay kits (DENLEY DRAGON Wellscan MK3; Thermo Fisher Scientific, Waltham, MA, USA). Peripheral venous blood samples for evaluation of the proportion of CD4^+ and $\text{CD4}^+/\text{CD8}^+$ cells were collected at baseline (t0), POD1 (t4), and POD3 (t5) by flow cytometry analyses on a BD FACSCalibur (BD Biosciences, Franklin Lakes, NJ, USA).

Statistical analysis

Data were processed using SPSS, Version 14.0 (SPSS Inc., Chicago, IL, USA). The data are expressed as mean \pm standard deviation. Levene's test was used for homogeneity of variances. We used one-way analysis of variance for propofol, remifentanyl, time to first flatus, and VAS score. Two-way analysis of variance was performed for other parameters. A *p*-value of <0.05 was considered statistically significant.

Results

In total, 120 patients undergoing laparoscopic rectal cancer surgery were included in this study. The four study groups comprised 30 patients each. No significant differences were found in age, sex, body mass index, duration of anesthesia, blood loss, albumin level, amount of intraoperative fluids, or complications (Tables 1 and 3).

The VAS scores at rest and on coughing of patients in the TAP groups (Groups A, B, and C) were lower than those of patients in Group D at t3 ($p < 0.01$) (Table 2). The VAS scores of patients in Groups B and C were lower than those in Groups A and D at t4 ($p < 0.01$) (Table 2). The VAS scores in

Groups B and C showed no significant difference at t3, t4, and t5 (Table 2).

Patients in Group D consumed more propofol, remifentanyl, and morphine than patients in the TAP groups (Groups A, B, and C) ($p < 0.01$) (Figure 1). Patients in Group A consumed more propofol, remifentanyl, and morphine than those in Groups B and C ($p < 0.01$) (Figure 1). There was no significant difference between Groups B and C (Figure 1). These results indicate that general anesthesia combined with a TAP block at an appropriate concentration reduces the anesthetic dose. The times to first flatus in Group A were significantly earlier than those in Group D ($p < 0.05$) (Figure 1). The times to first flatus in Groups B and C were significantly earlier than those in Groups A and D ($p < 0.01$) (Figure 1). The length of stay in the TAP groups was shorter than that in Group D ($p < 0.01$) (Figure 1). The length of stay in Groups B and C was shorter than that in Group A ($p < 0.01$) (Figure 1).

There were no statistically significant within-group differences in the basal level of epinephrine, Cor, IL-6, or TNF- α . The levels of epinephrine in the TAP groups were significantly lower than those in Group D at t1, t2, and t3 ($p < 0.01$)

Table 1. Characteristics and operation details of patients.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	Group D (n = 30)	<i>p</i>
Age (y) ^a	69.6 \pm 3.4	70.9 \pm 3.3	71.7 \pm 4.6	71.9 \pm 4.2	0.11
Sex (female/male) ^b	16/14	13/17	15/15	18/12	0.53
BMI (kg/m ²) ^a	22.2 \pm 2.8	24.0 \pm 2.9	23.2 \pm 2.3	23.4 \pm 3.1	0.09
Duration of anesthesia (min) ^a	166.4 \pm 10.4	161.7 \pm 4.6	164.1 \pm 9.3	161.8 \pm 6.1	0.08
Blood loss (mL) ^a	180.9 \pm 19.4	173.2 \pm 18.6	179.9 \pm 18.2	178.7 \pm 11.2	0.31
Albumin (g/L) ^a	33.9 \pm 3.3	34.6 \pm 3.05	33.3 \pm 2.94	33.4 \pm 3.1	0.35
Amount of intraoperative fluid (mL) ^a	696.7 \pm 68.1	712 \pm 66.5	714 \pm 61.8	731.3 \pm 46.5	0.19

Values are mean \pm standard deviation or number of patients. ^aAll *p* values for Levene's test were >0.1 ; ^b χ^2 test Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia; BMI = body mass index.

Table 2. Visual analogue scale scores at rest and on coughing.

	At rest			On coughing		
	t3	t4	t5	t3	t4	t5
Group A	3.5±0.5 ^{***#}	4.6±0.6 [#]	4.8±0.6	4.6±0.5 ^{***#}	5.0±0.6 [#]	5.2±0.5
Group B	2.3±0.5 ^{**}	3.0±0.5 ^{**}	4.7±0.6	3.3±0.5 ^{**}	4.0±0.5 ^{**}	5.1±0.6
Group C	2.0±0.6 ^{**}	2.6±0.5 ^{**}	4.6±0.5	3.0±0.6 ^{**}	3.9±0.4 ^{**}	5.0±0.6
Group D	4.9±0.7	4.3±0.7	4.7±0.7	5.4±0.4	5.1±0.7	5.3±0.5

Data are presented as mean ± standard deviation. Ordinary one-way analysis of variance was performed ^{**} $p < 0.01$ for value comparison with Group D. [#] $p < 0.01$ for value comparison between Groups B and C. Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia. t3 = tracheal extubation; t4 = postoperative day 1; t5 = postoperative day 3.

Table 3. Postoperative complications.

	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	Group D (n = 30)	<i>p</i>
Wound infection	2	3	3	2	0.93
Pneumonia	4	4	5	6	0.87
Gastric retention	3	3	4	3	0.96
Mortality	0	0	0	0	
Total (%)	9	10	12	11	0.86

Values are presented as percentage of patients

Data were analyzed by the chi-square test

Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia.

(Figure 2). The levels of epinephrine in Groups B and C were significantly lower than those in Group A at t1, t2, and t3 ($p < 0.01$) (Figure 2). There were no significant differences between Groups B and C at t1, t2, and t3 (Figure 2). The levels of Cor, IL-6, and TNF- α in Group A were significantly lower than those in Group D at t2 and t3 ($p < 0.05$) (Figure 2). The levels of Cor, IL-6, and TNF- α in Groups B and C were significantly lower than those in Groups A and D at t2 and t3 ($p < 0.01$) (Figure 2). There was no obvious difference between Groups B and C at any time point (Figure 2).

The proportions of CD4⁺ and CD4⁺/CD8⁺ cells were similar in all groups at t0. The proportions of CD4⁺ and CD4⁺/

CD8⁺ cells in Groups B and C were significantly higher than those in Group D at t4 and t5 ($p < 0.01$) (Figure 3). The proportions of CD4⁺ and CD4⁺/CD8⁺ cells in Groups B and C were significantly higher than those in Group A at t4 ($p < 0.05$) (Figure 3) and t5 ($p < 0.01$) (Figure 3). There was no obvious difference between Groups B and C at any time point (Figure 3). There was also no significant difference between Groups A and D at any time point (Figure 3).

Discussion

The results of this research indicate that the TAP block combined with general anesthesia plays a crucial role in fast-track surgery

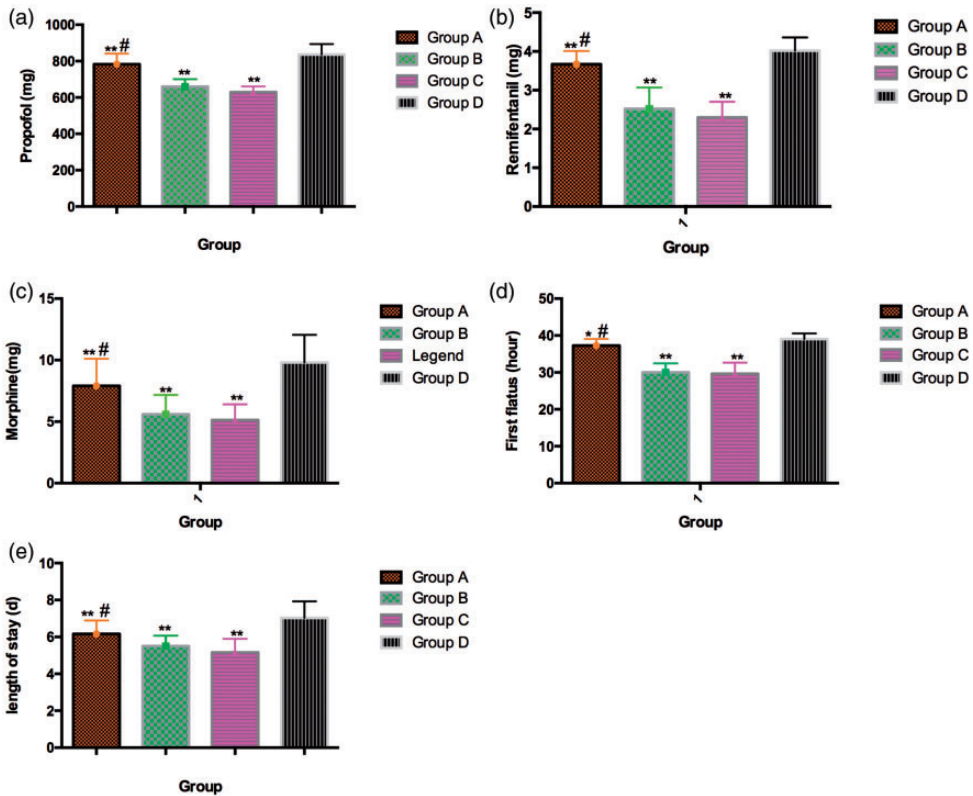


Figure 1. Consumption of propofol, remifentanyl, and morphine. Time to first flatus and length of stay. Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia. Data are expressed as mean \pm standard deviation. ** $p < 0.01$ compared with Group D. # $p < 0.01$ compared with Groups B and C.

in patients of advanced age undergoing laparoscopic rectal surgery. The stress response to the operation initiates a predictable series of metabolic and physiologic events by activating the somatic and sympathetic nervous systems.¹⁵ During the past several years, cytokines and stress hormones such as epinephrine and Cor have been identified as mediators of perioperative responses to surgery.^{16,17} Many clinical studies have shown that anti-inflammatory and proinflammatory cytokines are vital for the acute-phase immunologic and inflammatory response after surgical stress, and the most important of these cytokines are IL-6 and TNF- α .^{18,19} IL-6 is the principle

stimulus for acute responses, and the plasma level of IL-6 is reportedly associated with the severity of operational injury.²⁰ TNF- α is one of the primary cytokines that mediates the early reaction to tissue trauma.²¹ Plasma epinephrine in all groups of the present study significantly increased after the skin incision. The level of plasma epinephrine was significantly lower in the TAP groups than in Group D during surgery. The TAP block at a proper concentration seems to significantly reduce surgical stress. The levels of Cor, IL-6, and TNF- α were significantly higher in Group D than in the TAP groups from the time of the celiac exploration. Thus, the TAP block seemed to partially

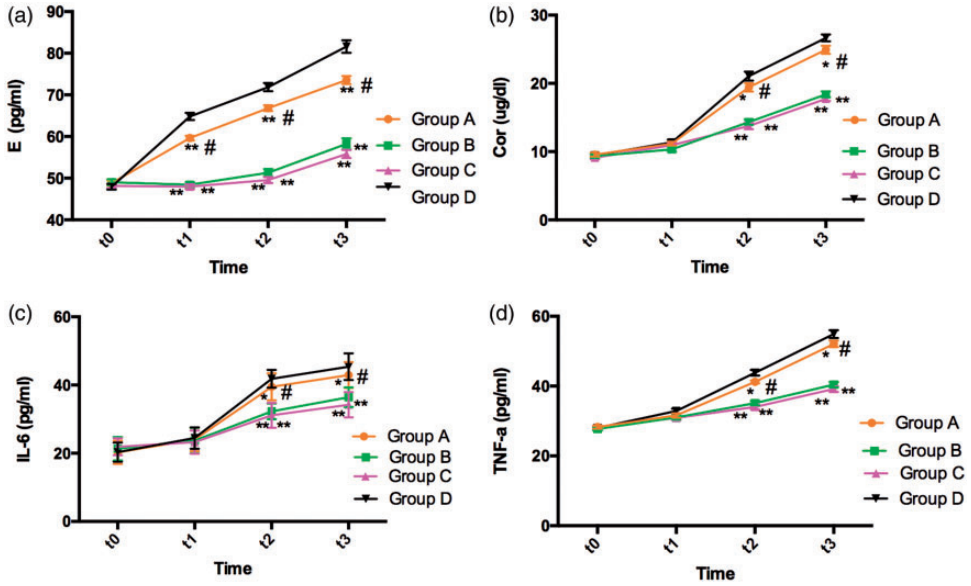


Figure 2. Plasma concentration of epinephrine (E), Cor, IL-6, and TNF- α . Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia. Data are expressed as mean \pm standard deviation. * $p < 0.05$ compared with Group D. ** $p < 0.01$ compared with Group D. # $p < 0.01$ compared with Groups B and C.

attenuate the surgical stress responses in our older patients undergoing laparoscopic rectal surgery.

One study revealed that psychological and physical stressors have an effect on lymphocyte subsets and function, which can alter the immune response.²² Another study suggested that the degree of physiological and psychological damage changed the immune system related to the stress response.²³ Stress can induce a decline in the CD4⁺ proportion and CD4⁺/CD8⁺ ratio. CD4⁺ T helper cells are an essential part of the human immune system, and one of their roles is to destroy infectious particles. A reduced CD4⁺/CD8⁺ ratio is associated with reduced resistance to infection. A declining CD4⁺/CD8⁺ ratio is associated with aging, which is an indicator of immunosenescence.²⁴ To reduce the incidence of infection and hospital cost, we should consider the high importance of immune function, especially in patients of

advanced age. In the present study, the CD4⁺ proportion and CD4⁺/CD8⁺ ratio were significantly lower in Group D than in Groups B and C. The concentration in Group A was not high enough to improve immune function. Overall, our study showed that the TAP block at an appropriate concentration can mitigate the surgical stress-related responses and immunosuppression in older patients undergoing laparoscopic rectal surgery.

Anesthetic drugs, particularly opioids, have immunosuppressive influences.⁶ In this study, all patients achieved a similar depth of anesthesia during the operation, while the TAP groups consumed significantly less propofol and remifentanyl. The total consumption of morphine was significantly lower in the TAP groups than in Group D. This may help to explain why the anti-tumor response can be protected by the TAP block in patients of advanced age. The mechanisms underlying the

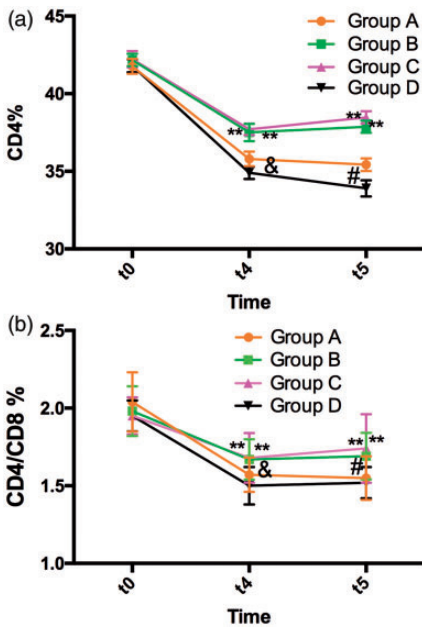


Figure 3. Lymphocyte subpopulations. Group A = 0.25% ropivacaine; Group B = 0.50% ropivacaine; Group C = 0.75% ropivacaine; Group D = general anesthesia. Data are expressed as mean \pm standard deviation. ** $p < 0.01$ compared with Group D. & $p < 0.05$ compared with Groups B and C. # $p < 0.01$ compared with Groups B and C.

widespread inhibition of intestinal motility are mainly related to intestinal dissemination of inflammation mediated by CD4⁺ T cells, endogenous opioids, and the surgical stress response secreted within the gastrointestinal tract during a reaction to operative trauma.^{25,26} Furthermore, opioids bind μ -opioid receptors in the central nervous system to mediate analgesia; however, opioids also bind to peripheral μ -opioid receptors in the gastrointestinal tract, leading to intestinal dysfunction and thereby exacerbating postoperative ileus.²⁷

In our study, the concentration of ropivacaine in Group A might not have been high enough to alter the immune response. The concentrations in Groups B and C had

a similar effect. Older patients with colon cancer often have hypoproteinemia, which raises the plasma concentration of ropivacaine and can increase the risk of a toxic reaction. Thus, the concentration of 0.50% ropivacaine may be better than 0.75% when used in patients of advanced age.

We are cognizant that our study had some limitations, mainly that the number of patients was small and the classification of the ropivacaine concentration was not detailed enough. Thus, further studies involving larger populations are needed, and a more detailed classification of the drug concentration may be more effective.

In conclusion, our study indicates that a proper concentration of ropivacaine in the TAP block plays an important role in anesthetic management in fast-track surgery protocols, especially in older patients undergoing rectal cancer surgery.

Author contributions

Conception and design: Qing-Song Lin, Ping-Chen. Acquisition of data: Ping-Chen. Analysis and interpretation of data: Ping-Chen. Drafting of the article: Ping-Chen. Critical revision of the article: Xian-Zhong Lin. Review of submitted version of manuscript: Qing-Song Lin. Statistical analysis: Ping-Chen. Administrative/technical/material support: Qing-Song Lin, Ping-Chen. Study supervision: Xian-Zhong Lin.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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