

Long-term results of retroperitoneoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma in China

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Abstract

Objective: We compared long-term clinical outcomes of upper urinary tract transitional cell carcinoma (TCC) patients treated by retroperitoneoscopic nephroureterectomy (RNU) or open radical nephroureterectomy (ONU).

Methods: Upper urinary tract TCC patients were treated with RNU (n = 86) or ONU (n = 72) and followed-up for more than three years. Demographic and clinical data, including preoperative indexes, intraoperative indexes and long-term clinical outcomes, were retrospectively compared to determine long-term efficacy of the two procedures.

Results: The RNU and ONU groups were statistically similar in age, gender, previous bladder cancer history, tumour location, pathologic tumour stage, pathologic node metastasis or tumour pathologic grade. The original surgery time required for both RNU and ONU was statistically similar, but RNU was associated with a significantly smaller volume of intraoperative estimated blood loss and shorter length of postoperative hospital stay. Follow-up (average: 42.4 months, range: 3-57) revealed that the RNU 3-year recurrence-free survival rate was 62.8% and the 3-year cancer specific survival rate was 80.7%. In the ONU group, the 3-year recurrence-free survival and the three-year cancer-specific survival rates were 59.2% and 80.3%, respectively. Neither of the survival rates were statistically different between the two groups. T stage, grade, lymph node metastasis and bladder tumour history were risk factors for tumour recurrence; the operation mode and the bladder cuff incision mode had no correlation with the recurrence-free survival.

Conclusion: The open surgery strategy and the retroperitoneoscopic nephroureterectomy strategy are equally effective for treating upper urinary tract TCC. However, the RNU procedure is less invasive, and requires a shorter duration of postoperative hospitalized care; thus, RNU is recommended as the preferred strategy.

Introduction

Upper urinary tract transitional cell carcinomas (TCC) are considered a relatively rare tumour type, and no internationally validated guidelines have been established for their treatment. Open radical nephroureterectomy (ONU), with the excision of a bladder cuff, represents the gold standard of treatment for upper urinary tract TCC. In the first large-scale, single-site, long-term retrospective study of upper urinary tract TCC, Hall and colleagues found that surgical intervention produced five-year disease-free survival rates of 100% for pTa, 91.7% for pT1, 72.6% for pT2, 40.5% for pT3, and 0% for pT4 tumours.¹ Over the past decade, however, the laparoscopic technique has emerged as the preferred method for surgical treatment of many cancers, including kidney and prostate, based on its minimally invasive nature and shorter recovery time. Accordingly, laparoscopic nephroureterectomy techniques (transperitoneal or retroperitoneal) have been developed to treat upper urinary tract TCC and are in clinical use worldwide. In 1991, Clayman and colleagues² reported the first laparoscopic nephroureterectomy; since then, several reports have been published that demonstrate superior short-term results and comparable oncologic outcomes of this procedure, as compared to open surgery.^{3,4}

Unfortunately, no randomized trials have been carried out to date and comparisons of the open and laparoscopic procedures are limited by differences in patient selection.⁵ The safety of laparoscopic nephroureterectomy has not yet been fully established,⁶ and the European Association of Urology (EUA) has suggested that laparoscopic procedures are only sufficiently effective in treating low-grade and stage tumours.⁷ ONU remains the recommended method for pT3 and pT4 tumours.⁵ To evaluate the long-term oncologic efficacy of retroperitoneoscopic nephroureterectomy (RNU), we designed a retrospective analysis of 158 patients with upper urinary tract TCC who had undergone ONU or RNU in China.

Methods

Clinical data

The electronic patient database of the First Bethune Hospital of Jilin University was queried for patients diagnosed with upper urinary tract TCC of the renal pelvis and ureter who had undergone radical nephroureterectomy and bladder cuff resection on-site. From January 2007 to January 2011, 158 consecutive patients with upper urinary tract TCC were enrolled in the study. All patients were diagnosed by intravenous urography, retrograde pyelography, computed tomography (CT) of the abdomen and ureteroscopy with or without biopsy. Preoperative cystoscopy and radiologic examinations were performed to rule out metastasis and concomitant bladder cancer. All patients received a regional lymph node dissection. The bladder cuff resection of all the patients who underwent ONU was performed by an open surgery. In the RNU group, the bladder cuff resection was performed via an endourologic approach or open surgery. The transurethral resection of the ureteral orifice was performed before the RNU, and the ureter was not clipped distally during the whole procedure. The Foley catheter was removed 4 to 5 days after the surgery. For patients who received an endourological approach, a cystogram was not needed before the removal of the Foley catheter. All patients received a postoperative intravesical adjuvant therapy to prevent urinary bladder recurrence.

Follow-up

Follow-up was carried out once every three months for the first three years, then every six months for the following two years, and annually thereafter. Follow-up consisted of history-taking, physical examination, hematocrit measurement, serum creatinine measurement, urinary cytology, chest radiograph, cystoscopic evaluation of the bladder and CT scan of the abdomen and pelvis. A bone scan, chest CT and magnetic resonance imaging were performed, if necessary. Disease recurrence was defined as local recurrence, intravesical recurrence and distant metastasis.

Statistical analysis

SPSS software (SAS Institute, Cary, NC) was used for all statistical analysis. Student's *t*-test or the Mann-Whitney test was used to compare continuous variables, while the Chi-square test was used to compare categorical variables. The Kaplan-Meier method was used to calculate survival rates. Tumour recurrence-free survival was defined as the interval from surgery to the first appearance of local or intravesical recurrence or distant metastasis. Univariable analysis was used to assess the risk factor to the tumour recurrence.

Covariables consisted of operation mode, T stage, grade, lymph node metastasis, bladder cuff incision mode and bladder tumour history. For all statistical tests, $p < 0.05$ was considered statistically significant.

Results

There were no significant differences in age, gender, bladder cancer history, tumour location, pathologic tumour

Table 1. Descriptive characteristics of patients treated with RNU or ONU for upper urinary tract carcinoma

Variables	RNU (n=86)	ONU (n=72)	<i>p</i> Value
Age (years)	68.7 (52–81)	66.1 (32–79)	0.78
Gender, n (%)			0.62
Male	49 (57.0)	43 (59.7)	
Female	37 (43.0)	27 (40.3)	
Tumour location, (%)			0.42
Renal pelvis	47 (54.7)	34 (47.2)	
Ureter	39 (45.3)	38 (52.8)	
Upper	9 (23.1)	11 (29.0)	
Middle	18 (46.2)	18 (47.4)	
Lower	12 (30.7)	9 (23.6)	
Previous bladder tumour, n (%)			0.18
Yes	5 (5.8)	8 (11.1)	
No	81 (94.2)	64 (88.9)	
pT stage, n (%)			0.48
pTa	3 (3.5)	2 (2.8)	
pT1	44 (51.2)	33 (45.8)	
pT2	31 (36.0)	26 (36.1)	
pT3	8 (9.3)	8 (11.1)	
pT4	0 (0)	3 (4.2)	
pN stage, n (%)			0.45
pN0	78 (90.7)	62 (86.1)	
pN1	8 (9.3)	10 (13.9)	
Grade, n (%)			0.87
Low	35 (41.7)	31 (43.1)	
High	51 (58.3)	41 (56.9)	
Bladder cuff resection, n (%)			<0.001
Endoscopy	34 (39.5)	0 (0)	
Open	52 (60.5)	72 (100)	
Surgical characteristics			
Mean operative time (min)	133.2±24.8	148.5±32.4	0.07
Mean estimate blood loss (mL)	176.3±21.2	286.1±31.2	<0.001
Transfusion, n (%)			0.66
Yes	2 (2.3)	3 (4.2)	
No	84 (97.7)	69 (95.8)	
Time to first diet (hour)	26.4±5.8	40.7±6.5	<0.001
Postoperative hospital stay (days)	5.5±1.6	7.3±2.6	<0.001

RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

Table 2. Univariable models predicting recurrence-free specific survival of upper urinary tract carcinoma after surgery

Variables	p value	Hazard ratio	95%CI
Operation mode			
RNU vs. ONU	0.87	1.06	0.68–1.58
pT stage			
T2 vs. Ta/T1	0.05	1.46	0.97–1.60
T3/T4 vs. Ta/T1	0.003	3.53	1.53–5.83
T3/T4 vs. T2	0.04	2.01	0.88–4.54
Grade			
High vs. Low	0.001	1.53	1.19–1.96
pN stage			
pN1 vs. pN0	<0.001	6.38	2.20–18.4
Previous bladder tumour			
Yes vs. No	0.04	2.91	1.01–8.48
Bladder cuff resection			
Endoscopy vs. Open	0.31	1.43	0.79–2.60

RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy; CI: confidence interval.

stage, pathologic lymph node metastasis or tumour pathologic grade between the two groups (Table 1). The bladder cuff resection of all the patients who underwent ONU was performed by an open surgery, and by the endoscopic approach for the 34 patients in the RNU group. The average operation time was 133 minutes for the RNU group and 148 minutes for the ONU group; the difference was not statistically significant. Two patients received blood transfusions when their intraoperative estimated blood loss surpassed 800 mL in the RNU group and the transfusion rate was 2.3%. The transfusion rate of ONU group was 4.2%, the differences had no statistical significance ($p = 0.66$). However, the intraoperative estimated blood loss in the RNU group showed a significant advantage (176.3 ± 21.2 mL vs. 286.1 ± 31.2 mL; $p < 0.001$). In addition, the time to the first meal (in hours) and postoperative hospital stay (in days) were significantly shorter in the RNU group than in the ONU group (26.4 ± 5.8 hours vs. 40.7 ± 6.5 hours and 5.5 ± 1.6 days vs. 7.3 ± 2.6 days, respectively; $p < 0.05$).

The median follow-up time was 42.4 months (range: 3 to 57). In the RNU group, 31 patients experienced a recurrence and 10 died of tumour relapse or metastasis. The RNU three-year recurrence-free survival rate was 62.8% and the three-year cancer specific survival rate was 80.7%. In the ONU group, 12 patients died of cancer and 25 patients had a tumour relapse; the three-year recurrence-free survival and the three-year cancer-specific survival rates were 59.2% and 80.3%, respectively. Neither of the survival rates was statistically different between the two groups (Fig. 1, Fig. 2). Intravesical recurrence occurred in 34 (RNU $n = 16$; ONU $n = 18$) patients. The three-year intravesical recurrence-free survival rate was 80.5% (RNU) and 72.8% (ONU); the recur-

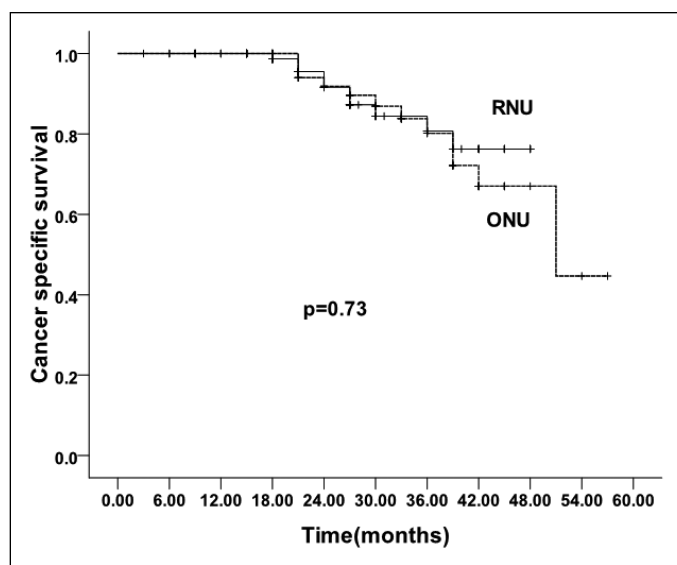


Fig. 1. Cancer specific survival rate stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

rence-free probabilities were similar between the two groups (Fig. 3). All of the intravesical recurrence occurred within 18 months after surgery and the mean recurrence time was 8.3 months; the difference between the two groups was not statistically significant (9.5 vs. 7.2 months; $p = 0.38$). After adjusting for tumour stage, no statistically significant differences with respect to recurrence-free survival were recorded for RNU versus ONU (Fig. 4, Fig. 5, Fig. 6).

In the univariable analysis, T stage, grade, lymph node metastasis and previous bladder tumour history were the risk factors that can influence the recurrence-free survival,

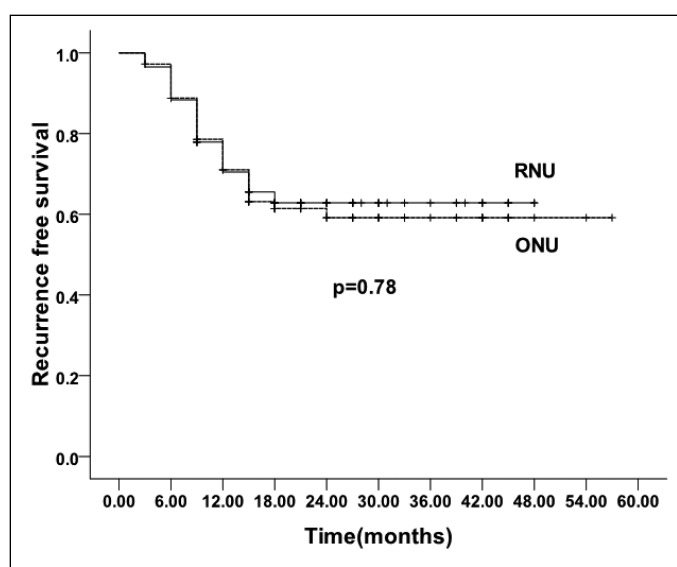


Fig. 2. Recurrence-free survival rate stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

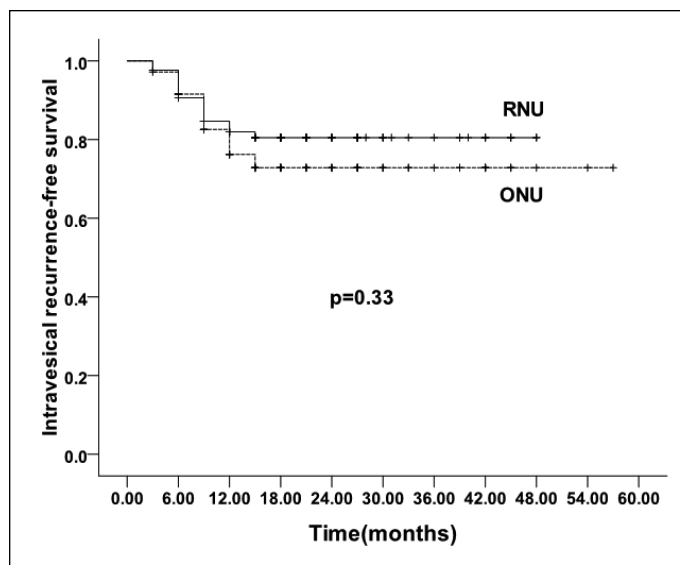


Fig. 3. Intravesical recurrence-free survival rate stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

and the operation mode and the bladder cuff incision mode had no relation with the recurrence-free survival (Hazard ratio [HR]:1.06, $p = 0.87$; HR:1.43, $p = 0.37$, respectively) (Table 2).

Discussion

Open nephroureterectomy and bladder cuff excision have been the standard treatment for upper urinary tract TCC. But with the wide application of laparoscopy in urology, laparoscopic nephroureterectomy has emerged as an excellent alternative to open surgery. The procedure can be performed via transperitoneal or retroperitoneal approach. In China, most urologists prefer to perform the operation via the retroperitoneal approach.

The general advantages of laparoscopic retroperitoneoscopic surgery are well-known. This minimally invasive technique is associated with quicker recovery and fewer complications, making the short-term result of retroperitoneoscopic surgery superior to open surgery.^{3,4,8} In our study, the mean operating time of RNU was slightly shorter than with the ONU, but the difference was not statistically significant ($p > 0.05$). Our surgical experience has indicated that the key factor influencing operation time is how quickly the renal artery is identified. Thus, as a surgeon accumulates experience, the operative time of RNU will decrease. On the other hand, the parameters of intraoperative estimated blood loss, postoperative hospital stay and recovery of intestinal function were significantly better in the RNU group. Our study showed that the short-term result of retroperitoneoscopic surgery is superior to open surgery; this conclusion is similar to those from other studies in China.^{9,10} However,

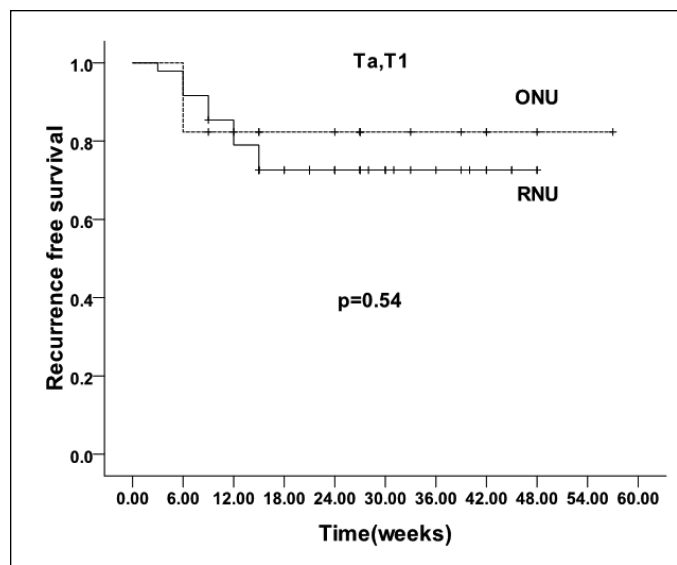


Fig. 4. Recurrence-free survival rate of Ta/T1 tumours stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

the postoperative hospital stay was longer than that was reported in Europe and the United States. The differences in health care systems may be the cause, as there are no differences in the techniques.

One of the most important features of urothelial carcinoma is the formation of tumours in multiple foci throughout the entire urinary tract. Bladder recurrence is common after surgical treatment, and the recurrence rate is between 15% and 50%.^{1,11-15} Previous studies have reported a positive correlation between laparoscopic-based treatment and intravesical recurrence, presumably due to downstream tumour shedding during the operation causing tumour implantation in intravesical spaces and/or inadequate distal bladder cuff excision owing to a limited working space.^{16,17} However, another study by Terakawa and colleagues indicated that the tumour stage and the presence of multiple tumours were the primary risk factors for bladder recurrence after nephroureterectomy.¹⁸ Finally, a retrospective study that did not adjust for tumour stage found that the operation mode had no influence on the bladder recurrence rate.¹⁹ In our series, 34 patients experienced bladder recurrence; 16 of these patients had received RNU treatment and 18 ONU treatment. The three-year intravesical recurrence-free survival rate was not significantly different between the treatment groups, indicating that the retroperitoneoscopic surgery did not increase the risk of bladder recurrence for upper urinary tract TCC.

Interestingly, all of the intravesical recurrence in our patients occurred within 18 months, and there was no correlation with treatment type. This indicates that the operation mode has no influence on the intravesical recurrence time. However, our patient population with intravesical recurrence was very small ($n = 34$); so these results may not

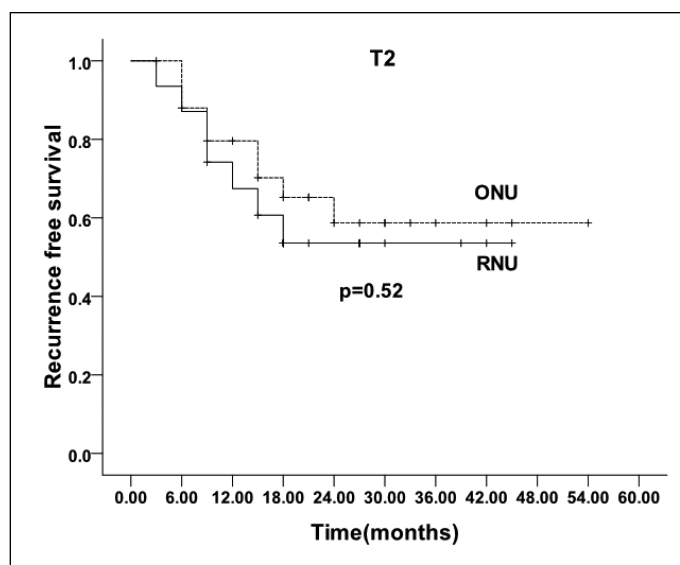


Fig. 5. Recurrence-free survival rate of T2 tumours stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

be generalizable. Hisataki and colleagues had previously investigated the excised tissues of 177 patients who underwent radical nephroureterectomy with bladder cuff excision; they found that 35.6% of patients developed urinary bladder intravesical recurrence within an average of 7.5 months, regardless of operation mode.¹⁵

Other authors reported that tumour grade and stage were the primary risk factors for prognosis, with no link to the mode of operation.²⁰ Capitanio and colleagues carried out a retrospective multicenter study, which included 1249 patients who underwent nephroureterectomy with bladder cuff excision.²¹ At follow-up, no statistically significant differences were observed for the recurrence rate or cancer-specific mortality between the two groups. Another retrospective study of 324 consecutive patients treated with radical nephroureterectomy found no evidence to indicate that oncologic control was differentially compromised in patients treated with laparoscopic surgery as compared to those treated with open surgery.²² Collectively, these results show that the laparoscopic procedure produces the same oncologic results in upper urinary tract TCC patients as the open surgery.

Similar to two other previous retrospective studies on upper urinary tract TCC treatment and recurrence,^{23,24} we find that the T stage, grade, lymph node metastasis and bladder tumour history are risk factors for tumour recurrence, and the operation mode and the bladder cuff incision mode has no correlation with the recurrence. In our cohort, the mean follow-up time was 42.4 months, and the three-year cancer specific survival rates was 80.7% in RNU group, and 80.3% in the ONU group, no statistically differences was observed. After adjustment for tumor stage; no statistically

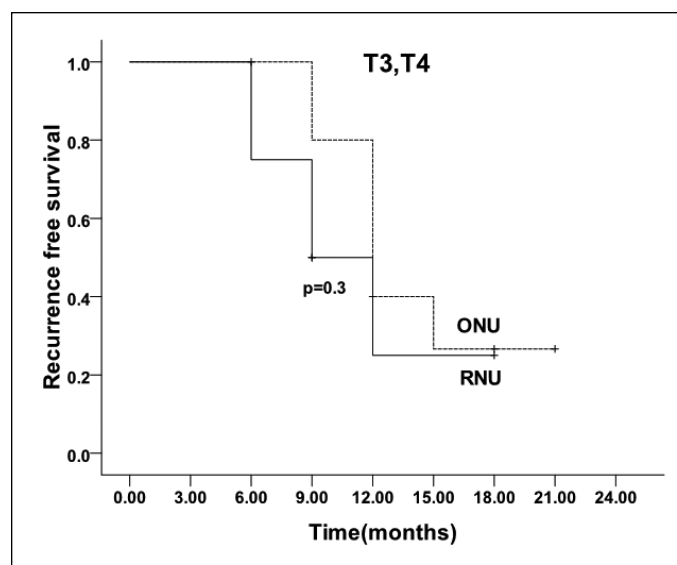


Fig. 6. Recurrence-free survival rate of T3/T4 tumours stratified by surgical approach. RNU: retroperitoneoscopic nephroureterectomy; ONU: open radical nephroureterectomy.

significant differences with respect to recurrence-free survival was recorded for RNU versus ONU. This suggests that the laparoscopic procedure does not increase the risk of tumour advancement or recurrence, and that it has the equivalent long-term oncologic results with the open surgery.

Conclusions

In our experience, retroperitoneoscopic nephroureterectomy represents a safe, minimally invasive and effective procedure to treat upper urinary tract TCC. RNU produces a superior short-term result and an equally beneficial oncologic result as the traditional open surgery mode. T stage, grade, lymph node metastasis and bladder tumour history are the risk factors for tumour recurrence, and the operation mode and the bladder cuff incision mode have no correlation with the recurrence-free survival. It is important to note, however, that the nature of the retrospective study design and the small sample sizes may limit the generalizability of our results. Further prospective randomized clinical trials are necessary to confirm our findings.

Competing interests: None declared.

This paper has been peer-reviewed.

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