Comparing survival after proximal gastrectomy vs. total gastrectomy in advanced gastric cancer: A systematic review and meta-analysis

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Abstract. The present systematic review and meta-analysis aimed to compare long-term survival after proximal gastrectomy (PG) and total gastrectomy (TG) for locally advanced proximal gastric cancer (GC). The PubMed, EMBASE and Cochrane CENTRAL databases were searched from their inception to May 2023. Only published two-arm prospective or retrospective studies were included. The selected studies included patients with locally advanced GC who underwent PG or TG and reported quantitative survival outcomes. The primary outcome was overall survival (OS) after gastrectomy. Three studies involving a total of 4,815 patients met the inclusion criteria. The age of the patients ranged from 57.03-64.46 years and 78.80% were male. The estimated 5-year OS probability after TG varied from 30.14 to 72.0%, and from 42.06 to 74.9% after PG. Results of the meta-analyses revealed a significant association between PG and improved OS compared with that of TG, with a pooled hazard ratio of 1.15 (95% CI, 1.05-1.25). No heterogeneity was observed in the included studies (I^2=0%). Overall, in managing locally advanced GC, PG demonstrated comparable or marginally improved OS compared with TG during postoperative follow-up; however, further meta-analyses are required to provide stronger evidence.

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-associated deaths worldwide, with ~1.08 million new cases and 769,000 deaths in 2020 (1). GC is classified into a cardia or non-cardia subtype based on a lesion site in either the upper (proximal) stomach nearest the heart or in the main (distal) part of the stomach, respectively (2,3). The gastric mucosa, or mucous membrane lining the stomach, comprises secretory glands and columnar epithelial cells that are prone to gastritis, a chronic inflammatory condition that may result in peptic ulcers and eventually lead to stomach cancer (4,5). Two distinct etiologies of cardia GC include one arising from obesity and gastroesophageal reflux disease (GERD), which occurs primarily in patients negative for *Helicobacter pylori* infection and resembles esophageal cancer, and another associated with *H. pylori* infection and chronic atrophic gastritis, resembling non-cardia GC (2,3,6). Risk factors for cardia GC include abdominal obesity, hiatal hernia, GERD and a high-fat, high-salt diet. Risk factors for non-cardia GC encompass *H. pylori* atrophic gastritis, which is responsible for the majority (90%) of non-cardia GC cases, as well as environmental factors, dietary considerations such as a high meat intake and a low intake of fruits and vegetables, and low socioeconomic status (2,3,6,7). While the incidence of GC has trended downward in certain countries over the past 50 years in association with efforts to eradicate *H. pylori* infection, a surge has been reported in the incidence of cardia GC located in the upper third of the stomach, particularly in eastern and central Asian countries, and Latin America (6,8-10). The change in GC subsites from distal to proximal has increased interest in the medical community regarding the treatment of proximal GC, particularly in selecting the most appropriate surgical approach, emphasizing the optimal extent of resection and the use of adjuvant therapy (10).

The surgical approaches commonly used for proximal GC include proximal gastrectomy (PG) and total gastrectomy (TG) (11). However, several studies that have explored the overall survival (OS) of patients with proximal GC who underwent either TG or PG have suggested that TG may be unnecessary for patients with proximal GC and that PG may be the optimal surgical approach, as the oncological outcomes and safety are comparable to those of TG (11-15). Nevertheless,

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since these studies focused either on early GC or did not specifically separate patients into early or locally advanced disease groups, the oncological viability of employing PG for addressing locally advanced lesions remains uncertain (16). Therefore, the present systematic review and meta-analysis aims to review the current evidence in the medical literature comparing the long-term postoperative survival rates between PG and TG for locally advanced proximal GC.

Materials and methods

Search strategy. The present systematic review and meta-analysis was conducted in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17). A literature search was conducted using three major public databases, namely, PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com/landing?status=grey) and Cochrane Central (https://www.cochranelibrary.com/central), using the key words 'advanced gastric cancer' and 'proximal gastrectomy' combined with Boolean operators, and by using Medical Subject-Heading terms where appropriate, for studies published up to May 1, 2023. For example, the search string used in PubMed was: (advanced gastric cancer) AND (proximal gastrectomy).

Additionally, the reference lists of the included studies were manually searched to identify other potentially relevant studies.

Selection criteria. The present systematic review and meta-analysis was performed in accordance with the PICOS criteria (18), which include participants (P), intervention (I), comparison (C), outcomes (O) and study design (S). Eligible studies were those that investigated patients with locally advanced GC who underwent PG or TG (P & I & C) and reported quantitative survival outcomes (O). Only published two-arm prospective and retrospective studies were considered (S).

Single-arm studies and those that did not report the quantitative outcomes of interest were excluded. Studies published in languages other than English were excluded from the analysis. The eligibility of the studies identified via the aforementioned search and selection strategy was confirmed by two independent reviewers, and a third reviewer was consulted when there was uncertainty regarding eligibility.

Main outcome measures and data extraction. The primary outcome was 5-year OS rate after gastrectomy. From the eligible studies, and when available, the following data were extracted: Name of the first author, year of publication, study design, type of surgery, number of patients, patients' mean age, sex (male %), pathological Tumor-Node-Metastasis stage (19), operative time, proportion of positive surgical margins, duration of follow-up, 5-year OS rate and hazard ratios (HRs) for OS.

Ethics statement. The present systematic review and meta-analysis of published studies neither required nor used raw patient data and private information; therefore, the Institutional Review Board (IRB) of National Cheng Kung University Hospital (Tainan, Taiwan) waived the requirement for approval of the protocol and informed consent from the study subjects.

Quality assessment. The quality of the non-randomized controlled trial (RCT) studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, as recommended by the Cochrane Non-Randomized Studies Methods Working Group (20,21). The NOS awards a maximum of nine points to each study, with four points awarded for the adequate selection of cohort participants, two points for the comparability of the cohort participants based on the design and analysis, and three points for the adequate ascertainment of outcomes. The quality of the non-RCT studies was assessed using the NOS, which awards a maximum of nine points to each study as follows: Four points for the selection of cohort participants, two points for the comparability of the cohorts and three points for the ascertainment of outcomes. Studies scoring 0-3 points were considered poor quality, those with 4-6 points were considered moderate quality and those with 7-9 points were considered good quality. Quality assessment was performed by two independent reviewers, and a third reviewer was consulted if any uncertainty occurred.

The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (22). GRADE evaluates evidence based on risk of bias, inconsistency, indirectness, imprecision and publication bias. The overall quality is categorized as high, moderate, low or very low, depending on how well the evidence meets these criteria.

Statistical analysis. As the study outcome was a time-to-event measure collected from every usable Cox model, adjusted HRs were determined for the effect size. Heterogeneity among the collected studies was evaluated using Cochran's Q test and I^2 statistics. Heterogeneity determined using the I^2 statistic was defined as follows: 0-24%, no heterogeneity; 25-49%, medium heterogeneity; 50-74%, high heterogeneity; and 75-100%, extremely high heterogeneity. The random effects model was applied in all analyses to account for the expected heterogeneity in intervention effects, which typically arises from diverse groups and geographical locations across multiple studies. Significance levels of two-sided tests were established as α=0.05. Publication bias was assessed by constructing funnel plots using Egger's test, with plots only generated for meta-analyses involving >10 studies due to the limited statistical power of fewer studies (23). However, since the study number included in this meta-analysis was <10, funnel plots were not generated. All analyses were performed using Comprehensive Meta-Analysis statistical software (version 2.0; Biostat, Inc.). $P<0.05$ was used to indicate a statistically significant difference.

Results

Study selection and characteristics. A flowchart of the process and results of the study selection are shown in Fig. 1. A total of 234 entries were found by searching the PubMed, CENTRAL and EMBASE databases, including a manual search. After screening titles and abstracts, and removing duplicates and irrelevant studies, the remaining six studies underwent full-text review based on the inclusion and exclusion criteria. Three articles were excluded as duplicates (n=1) or as mixed populations with early GC (n=2). Finally, three studies were included

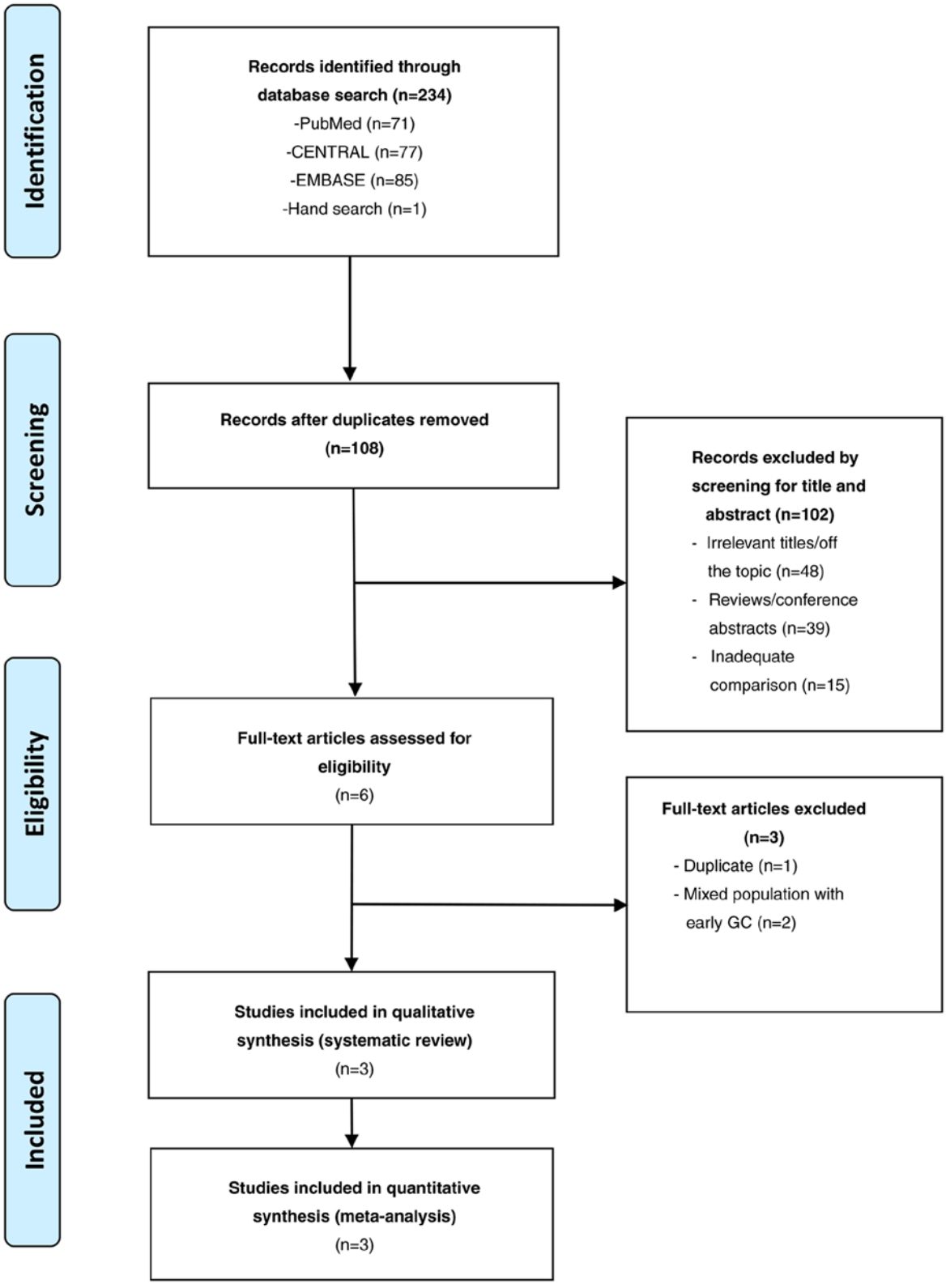

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of the study selection process. GC, gastric cancer.

in this meta-analysis (22-24), all of which had a retrospective design and included 4,815 patients.

Among the included studies, the study conducted by Tang *et al* (2020) (25) accounted for 91.0% of the samples. The age of the subjects ranged from 57.03 to 64.46 years and 78.80% were male. The estimated probability of 5-year OS after TG ranged from 30.14 to 72.0%, and from 42.06 to 74.9% after PG. The detailed data are presented in Table I.

Meta-analysis. Fig. 2 shows the results of the meta-analysis. The results revealed a significant pooled HR of 1.15 (95% CI, 1.05-1.25), suggesting that PG was superior to TG in terms

Table I. Characteristics of included studies.

First author, year	Study design	Total number of patients	Mean age, years	Male patients, %	Pathological TNM stage (I/II/III/IV), %	Operative time, min	Surgical margin-positive, %	Length of follow-up, months	5-year OS rate, %	NOS score	(Refs.)
Peng *et al*, 2022	Retrospective	134	64.46	71.6	TG: IB=28.4; IIA=16.4; IIB=29.9; IIIA=19.4; IIIB=6.0; IIIC=0.0	TG: 179.76±64.15	TG: 0	43 (4-84)[a]	TG: 64.3	7	(24)
					PG: IB=25.4; IIA=17.9; IIB=26.9; IIIA=26.9; IIIB=3.0; IIIC=0.0	PG: 167.15±43.73	PG: 0		PG: 74.9		
Zhao *et al*, 2020	Retrospective	300	57.03	84.67	TG: IB=6.00; II=39.33; III=54.67	TG: 213.5±66.7	TG: 6	TG: 45.9±5.6[b]	TG: 72.0	6	(26)
					PG: IB=5.33; II=32.67; III=62.00	PG: 181.8±49.8	PG: 2	PG: 62.7±3.5[b]	PG: 74.5		
Tang *et al*, 2020	Retrospective	4,381	64.43	78.62	TG: I=20.04; II=35.02; III=32.03; IV=0.00; Unknown=12.91	NA	TG: 13.05	Maximum 125+	TG: 30.1	6	(25)
					PG: I=26.07; II=34.67; III=23.09; IV=0.00; Unknown=16.17		PG: 9.98		PG: 42.1		

Data presented as [a]median (IQR) and [b]mean ± SE. TG, total gastrectomy; PG, proximal gastrectomy; OS, overall survival; NOS, Newcastle-Ottawa Scale; TNM, Tumor-Node-Metastasis; IQR, interquartile range; SE, standard error.

Table II. Characteristics of included studies using overall survival as the outcome.

Characteristic	Finding
No. of studies	3
Design	Observational studies
Risk of bias	Not serious
Inconsistency	Serious
Indirectness	Not serious
Imprecision	Not serious
Other	Publication bias strongly suspected
Certainty (overall score)	Very low

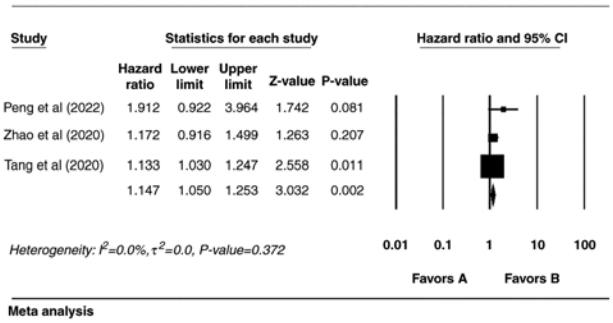

Figure 2. Meta-analysis of overall survival after TG vs. PG for locally advanced gastric cancer. CI, confidence interval; TG, total gastrectomy; PG, proximal gastrectomy.

of OS. Funnel plots were not generated owing to the limited number of available studies (<10). The small number of studies may not have provided sufficient statistical power to detect meaningful patterns, and the funnel plot may not accurately represent the underlying heterogeneity or publication bias, as described previously (21).

Risk of bias assessment and GRADE. The results of the risk of bias assessment of the individual studies by the NOS are listed in Table I. The three studies were of moderate-to-good quality. Nonetheless, the comprehensive assessment of the evidence in this meta-analysis based on the GRADE approach indicated a very low level of overall evidence quality, as shown in Table II.

Discussion

To the best of our knowledge, the present systematic review and meta-analysis is the first to review and compare the long-term survival after TG and PG for the treatment of locally advanced GC. The results revealed that PG was associated with a comparable or slightly better postoperative OS rate than TG. No heterogeneity was observed across the included studies, supporting these results.

Although the incidence and mortality rates of *H. pylori*-associated non-cardia GC have decreased in developed countries over the last five decades, corresponding to the eradication of *H. pylori*, the incidence of cardia GC occurring in the proximal stomach of *H. pylori*-negative individuals continues to increase (3,5,6). Such cases of proximal cardia cancer also continue to be deadly, and the debate about surgical approach, that is, whether patients with proximal cancer should undergo PG or TG, has not resulted in a consensus.

Addressing this issue by examining the long-term survival rates of patients with advanced proximal GC, the present meta-analysis showed that the differences in 5-year OS between the two surgeries were relatively modest. Three studies were selected to evaluate survival after PG and TG, and despite the small number of studies, there was a combined population size of 4,815 patients (1,462 with PG and 3,353 with TG), constituting a sizable sample for analysis. Among the three studies included in the meta-analysis, the results of the study by Peng *et al* (24) led the authors to conclude that PG was a reasonable choice for patients with proximal advanced GC and was specifically suitable for those with small tumors (<4 cm) and non-metastatic Borrmann type I/II or pathological stage T2/3 tumors. Zhao *et al* (26) selected patients with advanced GC treated with PG or TG from a large national database, and found no significant differences in mortality between the propensity score-matched surgery groups. The 3- and 5-year OS rates were slightly higher in the PG group than in the TG group, leading to the conclusion that the extent of resection did not influence the long-term outcomes.

However, rather than reporting no long-term differences in survival, the study by Tang *et al* (25), which had the largest study population, showed an improved survival benefit in patients undergoing PG compared with that in patients undergoing TG. Patient characteristics were a factor in the study, as among all the patients, those in the TG group had a poorer prognosis than those in the PG group, and patients receiving post-operative chemotherapy had a somewhat better long-term survival rate than those receiving surgery alone. It was suggested that the reasons for the differences in survival between PG and TG groups in this study compared with previous studies with no between-group differences (14,27,28) was that the earlier studies had lower percentages of poor tumor grades and did not control for confounding factors, such as adjuvant chemotherapy and radiotherapy, and the extent of lymphadenectomy (usually more complete in TG).

It is notable that one earlier meta-analysis (29) included mixed populations of patients with both early and locally advanced GC, which could confound the observations of survival outcomes after PG and TG. Nevertheless, a 2021 review of 25 studies and 2,896 patients with proximal GC examined perioperative outcomes, postoperative complications and long-term survival after PG and TG (10), reporting that PG had improved long-term survival outcomes compared with TG, and stratification by early and advanced GC had a similar result.

In addition to the contribution of genetics and family history, the lifetime risk of GC is influenced by age, *H. pylori* infection, obesity, tobacco smoking, alcohol consumption, diets high in salt and fatty meats, and insufficient consumption of fresh fruits and vegetables (6), as demonstrated in multiple earlier studies (5-7). The results of those studies suggest that risk stratification for GC must become integral to the clinical management of digestive issues leading to GC. Notably, subsets of proximal GC are categorized based on their specific

anatomical locations within the upper third of the stomach. Each location can significantly influence the behavior of the cancer, its symptoms, the treatment approach and, ultimately, survival rates. For instance, adenocarcinomas of the esophagogastric junction, particularly those classified as Siewert type II/III, may require more extensive surgical interventions due to their aggressive nature and complex lymphatic drainage patterns (30,31). However, further subgroup analyses based on these subsets were not feasible in the present meta-analysis, as the included studies lacked sufficient detail for comprehensive stratification.

As aforementioned, although existing meta-analyses have compared TG with PG, they have failed to distinguish between early and locally advanced diseases. This limitation underscores the novelty of the present meta-analysis, which contributes significantly to the literature by, to the best of our knowledge, being the first to specifically examine the prognosis of TG vs. PG in patients with locally advanced GC. No statistical heterogeneity was detected among the included studies (I^2=0%), which further strengthened the findings of this meta-analysis.

Nevertheless, the present meta-analysis had several limitations. First, the limited number of included studies may have affected the stability and reliability of the pooled results. This meta-analysis was based on three studies with markedly uneven case numbers (n=134, n=300 and n=4,381). Given this significant disparity, caution should be exercised when interpreting these results. In addition, while the pooled HR was derived from the adjusted HR values reported in each included study, which considered potential confounding factors such as patient demographic characteristics, the potential for unmeasured and unadjusted risk factors cannot be completely ruled out. Furthermore, the present meta-analysis focused only on OS rate, as it was the only available data; however, cancer-specific survival rate may provide more direct insights into long-term oncological outcome. Moreover, all the studies included in the present meta-analysis were retrospective in nature, which may have introduced a selection bias and compromised the reliability of the findings. Future meta-analyses should include more prospective or controlled trials to validate and corroborate the findings of the present study. Finally, there was an inability to conduct detailed subgroup analyses based on cancer stage, lymph node retrieval and chemotherapy modality. This was due to the lack of stratified survival outcomes provided by the included studies according to these specific characteristics. Further meta-analyses are recommended as more clinical reports become available to validate the findings of this study. Additionally, the included studies unanimously recommended conducting prospective RCTs to confirm their findings.

In conclusion, for the treatment of locally advanced GC, PG is associated with comparable or slightly better OS rates than TG at postoperative follow-up. Further meta-analyses, including the results of additional studies, are warranted to obtain more robust evidence.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PJS was responsible for conceptualization, data curation, formal analysis, writing the original draft, and reviewing and editing the manuscript. YTH, TKL WHL, CJW and YSS were responsible for conceptualization, data curation and formal analysis. YJC was responsible for the data curation, formal analysis, investigation and methodology of the study. All authors have read and approved the manuscript. PJS and YJC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This systematic review and meta-analysis of published studies neither required nor used raw patient data and private information; therefore, the Institutional Review Board of National Cheng Kung University Hospital (Tainan, Taiwan), waived the requirement for approval of the protocol and informed consent from study subjects.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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