# Impact of preoperative type 2 diabetes mellitus on the outcomes of patients with gastric cancer following gastrectomy: Analysis of 834 patients using propensity score matching

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**Abstract.** The purpose of the current study was to compare the outcomes of patients with gastric cancer (GC) between the type 2 diabetes mellitus (T2DM) group and the non-T2DM group. The PubMed, Embase and Cochrane Library databases were searched from inception to March 8, 2022, to identify propensity score matching (PSM) studies that analyzed the effect of T2DM on the outcomes of patients with GC. Total complications, overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS) were compared between the T2DM group and the non-T2DM group. A total of four PSM studies with 834 patients were included in the current study. There were 311 and 523 patients in the T2DM group and the non-T2DM group, respectively. Baseline characteristics of the two groups were adjusted with PSM in all the four studies, however, no significant difference was found in baseline characteristics (P>0.05). DFS was significantly worse in the T2DM group compared with that in the non-T2DM group [hazard ratio (HR), 1.45; 95% confidence interval (CI), 1.10-1.90; P=0.007)]. However, after pooling up the data, there was no significant difference between the T2DM group and the non-T2DM group in terms of OS (HR, 1.41; 95% CI, 0.92-2.16; P=0.11), CSS (HR, 1.29; 95% CI, 0.92-1.81; P=0.14) and total complications (odds ratio, 1.01; 95% CI, 0.64-1.60; P=0.95). Patients with GC and T2DM are associated with poor DFS. However, there were no significant differences between the T2DM group and the non-T2DM group in terms of OS, CSS and total complications.

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*Abbreviations:* GC, gastric cancer; T2DM, type 2 diabetes mellitus; PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; HR, hazard ratio; OR, odds ratio; NOS, Newcastle-Ottawa Scale; MD, mean difference; CI, confidence interval

*Key words:* gastric cancer, type 2 diabetes mellitus, propensity score matching, outcomes

## Introduction

Gastric cancer (GC) has the 5th highest incidence of all cancers worldwide, and it is the 3rd leading cause of cancer-related death (1,2). The clarity mechanism leading to the tumorigenesis and progress of GC is still unknown. There are certain factors which play an important role in the development of GC, with Helicobacter pylori (HP) being the main one (3). Contrary to Western countries, numerous countries in Asia, such as Japan, are more affected by HP (4).

Type 2 diabetes mellitus (T2DM) is also one of the leading causes of death in the world (5), and the incidence of this disease has gradually increased over the years. By 2045, the prevalence of diabetes is expected to be 21.1% in middle-income countries (6). T2DM can increase the risk of cardiovascular disease (7,8), and it is positively associated with the incidence of GC (9,10). A previous prospective study showed that hyperglycemia was an independent risk factor of GC (11). Although the mechanism remains unclear, hyperglycemia is more common in patients with T2DM, which could increase the risk of GC. Therefore, it is apparent that there is a close relationship between T2DM and GC.

The impact of T2DM on the outcomes of patients with GC following gastrectomy remains controversial (12,13), and there is a need to analyze the long-term outcomes of patients with GC between the T2DM group and the non-T2DM group. Previous studies which analyzed the relationship between GC and T2DM could have been affected by selection biases (9,10). The propensity score matching (PSM) method could reduce selection bias in terms of covariates, such as sex and age (14,15).

Therefore, the aim of the current study was to analyze the outcomes of patients with GC in the T2DM group and the non-T2DM group.

## Materials and methods

*Search strategy*. The PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com/landing?status=grey)

Table I. Characteristics of included studies.

| First author, year | Country | Time quantum, year.month | Center | Design | Analysis | Simple size before matching, n | | Simple size after matching, n | | NOS score | (Refs.) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | DM | Non-DM | DM | Non-DM | | |
| Matsui *et al*, 2022 | Japan | 2008.4-2018.6 | Single | Retrospective | PSM | 92 | 420 | 72 | 216 | 7 | (19) |
| Sheng *et al*, 2020 | China | 2008.11-2015.12 | Single | Retrospective | PSM | 84 | 215 | 84 | 84 | 8 | (20) |
| Chen *et al*, 2020 | China | 2004.4-2015.12 | Single | Retrospective | PSM | 71 | 1621 | 71 | 139 | 7 | (13) |
| Cheng *et al*, 2022 | China | 2014.1-2019.12 | Single | Retrospective | PSM | 84 | 619 | 84 | 84 | 8 | (21) |

NOS, Newcastle-Ottawa Scale; PSM, propensity score matching; DM, diabetes mellitus.

and Cochrane Library (https://www.cochranelibrary.com) databases were searched from inception to March 8, 2022, to identify eligible studies for inclusion in the present study. The search strategy for GC was as follows: 'Stomach tumor' OR 'stomach neoplasm' OR 'stomach cancer' OR 'cancer of the stomach' OR 'gastric neoplasm' OR 'gastric cancer'. The search strategy for T2DM was as follows: 'Diabetes' OR 'type 2 diabetes' OR 'diabetes mellitus'.

The search strategy used complied with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses published in 2009 (16). The PICO criteria used in the present study were: i) Patients (P), patients with GC who underwent gastrectomy; ii) intervention (I), patients with GC and T2DM; iii) comparison (C), patients with GC but without T2DM; and iv) outcome (O), outcomes of patients with GC with or without T2DM, such as complications, OS and DFS.

*Inclusion and exclusion criteria*. The inclusion criteria were as follows: i) Studies that used PSM analysis; ii) studies that provided data suitable for the evaluation of outcomes, such as total complications, overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS); iii) studies that provided data allowing calculation of either the hazard ratio (HR) or the odds ratio (OR) with 95% confidence interval (CI) (4); and iv) studies that provided the sample size and other appropriate data, such as sex, age, complications and surgery information.

The exclusion criteria were: i) Non-reporting of predefined outcomes for patients with GC in the T2DM group and the non-T2DM group, or inability to extract the number of outcome events from the published results; ii) articles that were considered letters, commentaries, correspondences, editorials and reviews, including meta-analyses; and iii) retrospective studies that had no matched control which used PSM to eliminate the effect of covariates.

*Study selection and data extraction*. The databases were independently searched by two reviewers, and duplicate records were removed. After titles and abstracts were screened, full texts were evaluated based on the aforementioned inclusion, exclusion and PICO criteria. Two reviewers conducted the study selection, and any disagreements were resolved by group discussion and consensus.

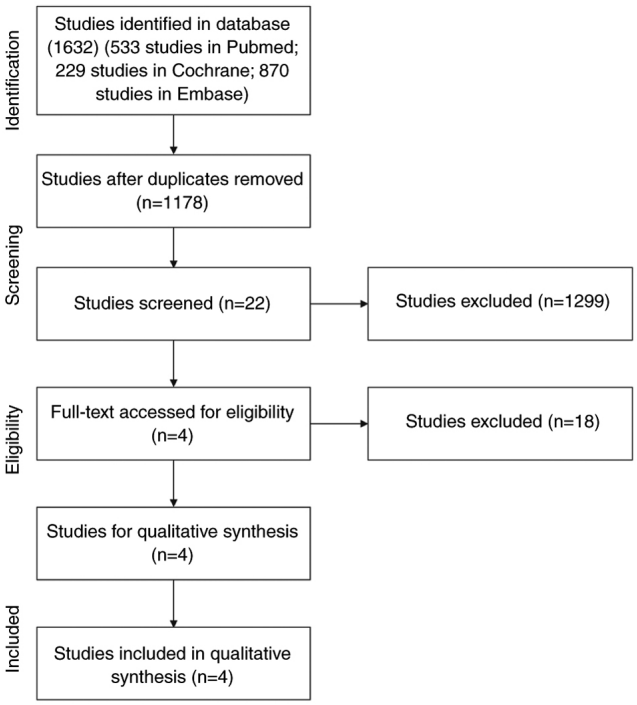


Figure 1. Flowchart of study selection.

The data were extracted and cross-checked by two reviewers who extracted the following information from every eligible study: First author, country, year, time quantum, center, study design, type of analysis, sample size before and after matching, baseline information, surgical information, postoperative total complications and survival information. If the required data could not be extracted from a study, the

Table II. Summary of information between the DM group and the non-DM group.

| Characteristics | Studies, n | Patients with DM/non-DM, n | Mean difference | | Heterogeneity | |
|---|---|---|---|---|---|---|
| | | | OR (95% CI) | P-value | $I^2$ (%) | P-value |
| Sex | | | | | | |
| Male | 4 | 213/367 | 0.95 (0.70-1.30) | 0.76 | 0 | 0.89 |
| Female | 4 | 98/156 | 1.05 (0.77-1.44) | 0.76 | 0 | 0.89 |
| Age, years | 3 | 240/384 | 0.47 (-1.12-2.05) | 0.56 | 0 | 0.73 |
| BMI, kg/m$^2$ | 2 | 156/230 | 0.15 (-0.53-0.83) | 0.66 | 0 | 0.68 |
| Pathological stage | | | | | | |
| I-II | 3 | 106/187 | 0.99 (0.70-1.38) | 0.93 | 0 | 0.74 |
| III-IV | 3 | 134/197 | 1.02 (0.72-1.43) | 0.93 | 0 | 0.74 |
| Surgical procedure | | | | | | |
| Subtotal gastrectomy | 3 | 146/282 | 1.00 (0.71-1.41) | 0.98 | 0 | 0.42 |
| Total gastrectomy | 3 | 81/157 | 1.00 (0.71-1.40) | 0.98 | 0 | 0.42 |
| Chemotherapy | 2 | 76/116 | 0.58 (0.20-1.71) | 0.33 | 0 | 0.06 |
| Surgical approach | | | | | | |
| Laparoscopic surgery | 3 | 159/286 | 0.87 (0.59-1.27) | 0.46 | 0 | 0.84 |
| Open surgery | 3 | 68/153 | 1.15 (0.79-1.69) | 0.46 | 0 | 0.84 |
| Reconstruction methods | | | | | | |
| Roux Y | 3 | 112/239 | 1.01 (0.71-1.43) | 0.95 | 0 | 0.68 |
| Others | 3 | 115/200 | 0.99 (0.70-1.40) | 0.95 | 0 | 0.68 |
| Total complications | 2 | 42/74 | 1.01 (0.64-1.60) | 0.95 | 0 | 0.45 |

DM, diabetes mellitus; CI, confidence interval; OR, odds ratio.

original authors of that study were conducted directly, whenever possible.

*Quality assessment*. The Newcastle-Ottawa Scale (NOS) scoring system was used to independently assess the quality of the four studies selected by the two reviewers (17). The maximum scale was 9 points. Studies of high quality scored 9 points, studies of medium quality scored 7-8 points, and studies of low quality scored <7 points (18).

*Data synthesis and statistical analysis*. Review Manager (version 5.4; The Cochrane Collaboration) was used in the present study. Statistical heterogeneity was assessed by the $I^2$ value and the result of the $\chi^2$ test. When $I^2$>50%, a fixed-effects model was used. By contrast, when $I^2$≤50%, a random-effects model was used and the tau$^2$ value was calculated.

For dichotomous and continuous variables, OR, mean difference (MD) and 95% CI were calculated. The pooled HR and the 95% CI of every study were calculated to estimate the survival outcomes.

Statistical heterogeneity was calculated using the $I^2$ statistic, which determined the proportion of total variation across studies that was due to heterogeneity rather than chance. Forest plots were shown in order by weight for every study. P<0.05 was considered to indicate a statistically significant significance. Meanwhile, the Z-score was calculated to measure the relative position of the sample data of the present study in the population; therefore, it was determined whether data were considered an outlier.

## Results

*Study identification and eligibility*. A total of 1,632 studies were identified after electronic search, of which 533, 229 and 870 studies were identified in PubMed, Cochrane and Embase databases, respectively. A total of 454 studies were regarded as duplicates based on title search. Based on the selection and PICO criteria, there were 22 studies remaining, which were accessed by full-text scanning, with four studies being eligible for inclusion in the present study (13,19-21). After PSM, a total of 834 patients were included. A flow diagram of the analysis protocol is shown in Fig. 1.

*Characteristics of the included studies*. Three studies originated from China, and one study originated from Japan. The publication year of the four included studies ranged from 2020 to 2022. The time quantum was from April 2008 to December 2019. The characteristics and detailed information of the sample size of the four included studies are shown in Table I. Although the four studies were retrospective, single-center studies, PSM analysis was used.

*Data adjustment in the included studies*. The summary of the information in the T2DM group and the non-T2DM group is shown in Table II. There were no significant differences

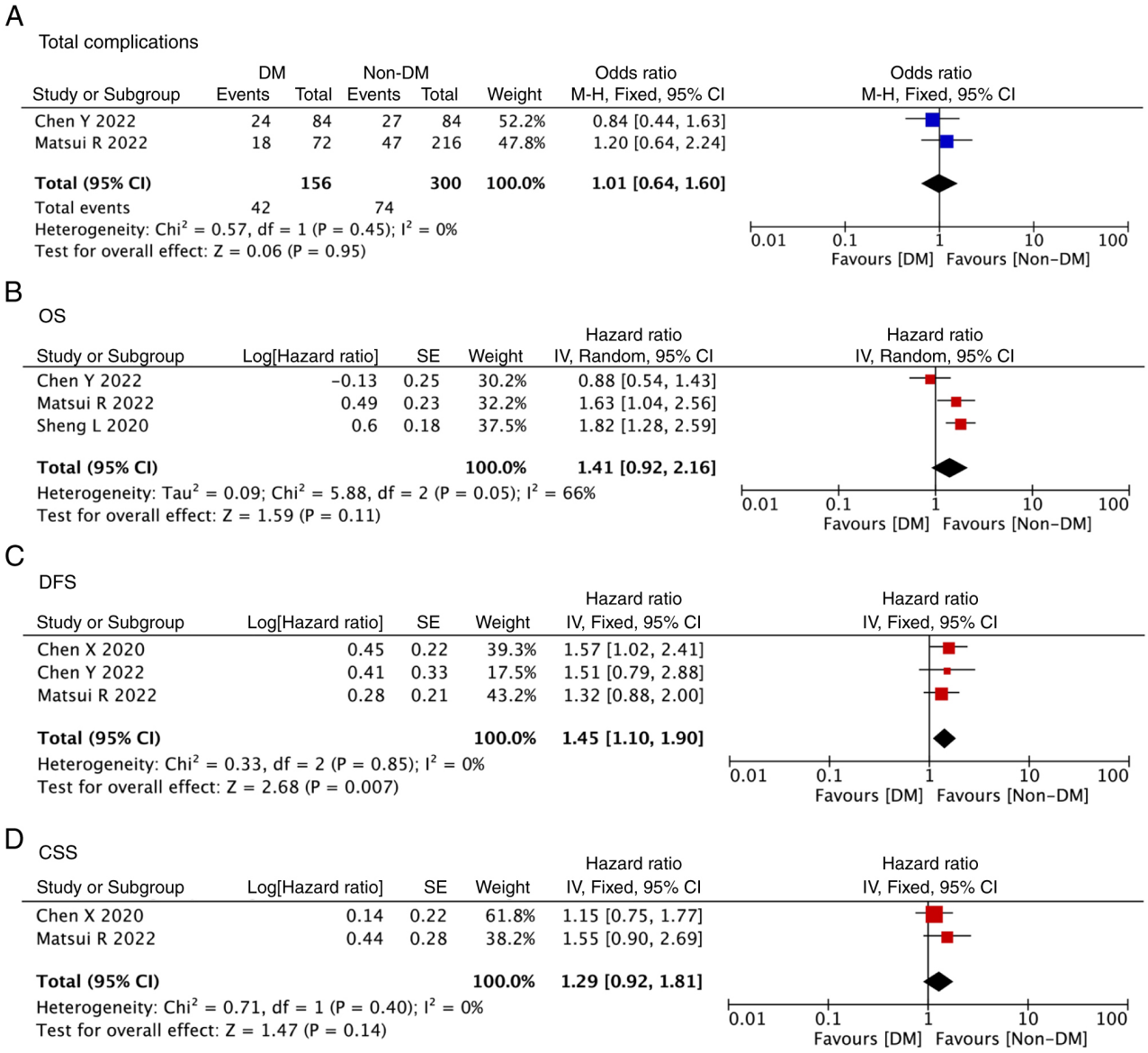


Figure 2. Forest plot showing the outcomes of patients with GC between the T2DM group and the non-T2DM group. (A) Total complications, (B) OS, (C) DFS and (D) CSS of patients with GC between the T2DM group and the non-T2DM group. T2DM, type 2 diabetes mellitus; GC, gastric cancer; OS, overall survival; DFS, disease-free survival; CSS, cancer-specific survival; CI, confidence interval; DM, diabetes mellitus; df, degrees of freedom.

between the T2DM group and the non-T2DM group in either of the four studies or the current study.

*Quality of included studies*. All four included studies were assessed using the NOS scoring system, and the results are shown in Table I.

*Association between T2DM and outcomes*. Data on total complications were available for two studies (19,21). After pooling up the data, there were no significant differences between the T2DM group and the non-T2DM group (OR, 1.01; 95% CI, 0.64-1.60; P=0.95; Fig. 2A).

A total of three studies included data on OS (19-21), three studies included data on DFS (13,19,21), and two studies included data on CSS (13,19). The DFS in the T2DM group was significantly worse than that in the non-T2DM group (HR, 1.45; 95% CI, 1.10-1.90; P=0.007; Fig. 2C). However, after pooling up the data, there were no significant differences between the T2DM group and the non-T2DM group in terms of OS (HR, 1.41; 95% CI, 0.92-2.16; P=0.11; Fig. 2B) and CSS (HR, 1.29; 95% CI, 0.92-1.81; P=0.14; Fig. 2D).

## Discussion

Research in GC has increased due to the high incidence and mortality of the disease (1,2). HP infection has been recognized as an important factor of GC (3). Only a fraction of individuals with HP infection developed GC, which showed that HP infection was not an independent etiologic factor of GC (22). Ikeda *et al* (11) showed that hyperglycemia might enhance the ability of HP to cause GC. This finding indicates the close relationship between T2DM and GC.

Numerous studies investigated the association of T2DM with GC regarding patient outcomes, and a meta-analysis discussed the controversial results of those studies (9,12,22). However, in terms of survival, the meta-analytic study only

discussed the risk of the incidence and mortality of patients with GC and DM; the association of OS, DFS and CSS was not involved. Additionally, the included studies of the present meta-analysis did not uniform the baseline information by PSM (22). Therefore, the current meta-analysis that included four studies using PSM (13,19-21) could assist in reducing selection biases (17,18). Furthermore, more detailed data, including complications, OS, DFS and CSS were analyzed. A total of 834 patients were included in the current meta-analysis. There were 311 and 523 patients in the T2DM group and the non-T2DM group, respectively. The baseline characteristics of the two groups were adjusted using PSM in all the four included studies. After pooling up the data, the DFS in the T2DM group was significantly worse than that in the non-T2DM group. However, no significant difference was found between the T2DM group and the non-T2DM group in terms of OS, CSS and total complications.

The exact link between GC and T2DM is still debated. Some studies hypothesized that T2DM might influence the prognosis of patients with GC in terms of OS, DFS and CSS (15,20). However, other studies reported no significant relationship between T2DM and GC in terms of prognosis (23,24). Therefore, the impact of T2DM on the outcomes of patients with GC after gastrectomy remains controversial (14,17). It is essential to compare the long-term outcomes of patients with GC in the T2DM group and the non-T2DM group. Moreover, there were a few studies discussing the outcomes of patients with GC after gastrectomy between the T2DM group and the non-T2DM group through PSM (13,19-21). The current meta-analysis included four of those studies using PSM to explore the postoperative outcomes of patients with GC between the T2DM group and the non-T2DM group (13,19-21).

Zylla *et al* (25) reported that T2DM was associated with higher infection and readmission rates. Other studies also showed that T2DM was associated with increased postoperative complications, for example, anastomotic leakage and hemorrhage (12,25,26). The possible mechanism was as follows: i) Glycolysis is highly dependent on glucose, and a number of tumour cells rely on glycolysis for energy supply while in the state of hyperglycemia, making uncontrolled hyperglycemia beneficial to cancer cell proliferation (27); and ii) chronic inflammatory disease, such as T2DM, may result in malignant tumors (28). However, in the present study, after pooling up the data, it was shown that there was no significant difference in complications between the T2DM group and the non-T2DM group.

Chen *et al* (13), as well as other studies with (20) and without PSM (12), reported that T2DM could lead to worse OS. While more studies with PSM showed that there were no significant differences in OS (19,21), in the current study, T2DM was associated with worse OS, but the difference was not statistically significant. The meta-analysis by Tian *et al* (22) showed that DM lead to higher mortality in patients with GC, which is different from what was found in the present study. A possible explanation for the discrepancy could be that the study by Tian *et al* (22) did not distinguish T1DM from T2DM. Evidence suggested that individuals with T1DM had higher risk of GC than T2DM (29). Chen *et al* (13) hypothesized that T2DM was associated with worse DFS, which was different to the hypothesis in two other studies (20,21). The current study showed that T2DM was related to significantly worse DFS. It seemed there was a contradictory result between OS and DFS. T2DM has a significant relationship with worse DFS, but OS was similar in the T2DM group and the non-T2DM group. Therefore, a larger-data prospective study would enable the investigation of the exact impact of T2DM on the prognosis of patients with GC. Regarding CSS, all the studies included in the present study showed that there was no significant difference between the T2DM group and the non-T2DM group.

All the four studies included in the current study originated from Asian countries; three originated from China and one from Japan. There is probably a connection with the high incidence of GC in Asian countries, including China, Japan and Korea (30). Three out of the four of studies included in the present study showed a significant correlation between T2DM and prognosis in GC, which was consistent with previous studies (21,31,32). By contrast, the incidence of GC in Western countries and the association between GC and T2DM are poorer. The possible explanation may be related to the difference in ethnic backgrounds and dietary habits.

However, some baseline information could not be analyzed. Because the baseline characteristics of the four studies were inconsistent. For example, coronary heart disease, chronic obstructive pulmonary disease, lymph node dissection and other-cause survival could not be analyzed.

To the best of our knowledge, the current study is the first meta-analysis that included only PSM studies. The PSM method can reduce the selection biases such as age and sex, and the inconformity of baseline information (14,15), which could increase the credibility of the present meta-analysis.

The present meta-analysis also has several limitations. Firstly, although all connected PSM studies had been selected, the number of studies selected for inclusion was relatively small. Secondly, all four included studies were single-center, retrospective studies. Thirdly, none of the studies described all the aforementioned measures of postoperative survival. Fourthly, the data on total complications were identified in only two studies. Fifthly, all the four studies originated from Asian countries, therefore, results could be ethic origin-specific. Additional multi-center, prospective, worldwide studies are needed.

To sum up, patients with GC and T2DM show poor DFS. However, there were no significant differences between the T2DM group and the non-T2DM group in terms of OS, CSS and total complications.

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**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Authors' contributions**

YQ carried out literature search, prepared the figures, completed the study design, performed data collection, analysis and interpretation, and wrote the manuscript. DP carried out literature search, and data collection, analysis and interpretation. KT completed the study design, carried out data interpretation and wrote the manuscript. YX wrote and revised the manuscript. All authors read and approved the final version of the 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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