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Sub-Staging-Specific Differences in Recurrence-Free, Progression-Free, and Cancer-Specific Survival for Patients with T1 Bladder Cancer: A Systematic Review and Meta-Analysis

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Keywords
Urinary bladder neoplasms · Sub-staging · Muscularis mucosa · Progression · Recurrence · Cancer-specific survival

Abstract
Introduction: The efficiency of the T1 sub-staging system on categorizing bladder cancer (BC) patients into subgroups with different clinical outcomes was unclear. We summarized relevant evidences, including recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS), to analyze the prognostic significance of T1 sub-stage. ***Methods:*** Systematic literature searches of MEDLINE, EMBASE, and the Cochrane Library were performed. We pooled data on recurrence, progression, and CSS from 35 studies. ***Results:*** The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) indicated the difference in RFS between T1a sub-stage and T1b sub-stage (HR 1.28, 95% CI 1.14–1.43, $p < 0.001$). The significant difference was observed in PFS between the 2 arms (HR 2.18, 95% CI 1.95–2.44, $p < 0.001$). Worse CSS was found in T1b patients than in T1a patients (HR 1.36, 95% CI 1.21–1.54, $p < 0.001$). ***Conclusions:*** T1 sub-staging system based on the invasion depth into muscularis mucosae can be a significant prognostic factor for RFS, PFS, and CSS of patients with T1 BC. Urologists and pathologists are encouraged to work together to give a precise sub-stage classification of T1 BC, and T1 sub-staging system should be a routine part of any histopathological report when possible. Different treatment strategies need to be developed for both T1a BC and T1b BC.

Introduction

Up to 75% of bladder cancers (BCs) are non-muscle invasive at initial diagnosis. T1 BC, which invades the lamina propria but not the muscularis propria, comprises 20% of non-muscle invasive BC [1]. And the prognostic situation is challenging, related to the relatively high 5-year recurrence rates (39–45%), 5-year progression rates (18–23%), and the cancer-specific mortality (15%) [2]. Therefore, some experts recommended that radical cystectomy should be performed for all T1 BC patients [3], while some experts believed that radical cystectomy was an unnecessary treatment strategy for nonprogressive T1 BC and negatively affected the quality of life [4]. However, the predictive value of TNM stage is limited in

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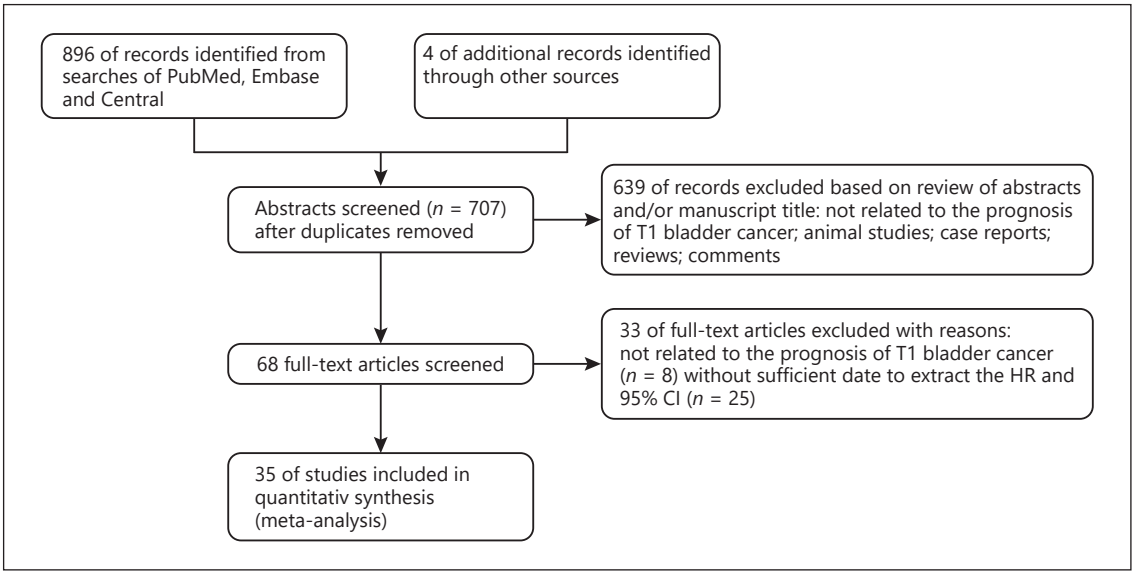

Fig. 1. Study flow chart. A total of 35 studies met the inclusion criteria.

T1 BC. The T1 sub-stage may help categorize patients into different subgroups with different clinical outcomes, and T1 sub-stage has been identified as an important prognostic factor. The most widely studied sub-staging system for T1 BC is based on muscularis mucosae (MM) invasion. The MM is a discontinuous layer of smooth muscle bundles, approximately situated in the middle between the urothelium and the muscularis propria. Two invasion stages can be defined as invasion above the MM (referred as T1a) and invasion in or through the MM (referred as T1b). The main objective of this review was to analyze the prognostic significance of T1 sub-staging system based on MM invasion in recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS) for T1 BC patients.

Methods

Data Sources and Searches

A research librarian searched multiple electronic databases, including MEDLINE, EMBASE, and the Cochrane Library in September 2018. The full search algorithm is shown in online suppl. word; see www.karger.com/doi/10.1159/000506238 for all online suppl. material. We also reviewed reference lists and previous systematic reviews for additional studies and searched documents for unpublished studies.

Study Selection

The inclusion criteria were as follows: First, the participants must be identified as T1 primary BC patients. Second, the category was according to T1 sub-staging system based on MM invasion. Third, the predefined outcomes were differences in RFS, PFS, and CSS between T1a and T1b. Publications were required to report hazard ratios (HRs) and 95% confidence intervals (CIs) or documented data, which allowed an HR to be readily calculable for one of the specified outcomes [5]. The recurrence was defined as histological detection of BC after 3 months of transurethral resection of bladder tumor (TURBT). The progression was defined as later occurrence of any higher stage disease. Two reviewers evaluated each study on the basis of predefined inclusion criteria. Only studies which fulfilled inclusion criteria, evaluation of at least one outcome (RFS, PFS, or CSS) after TURBT, were included. Case reports, review articles, and meta-analyses were excluded.

Data Extraction and Study Quality Assessment

Two reviewers extracted data on baseline characteristics, methods, and outcomes (HRs, number of events for recurrence, progression, and CSS) from included articles. The disagreements were resolved by consensus. We used the Newcastle-Ottawa Scale system to rate the quality of all studies. Studies with scores more than 7 were assessed as "low risk," scores of 4–6 were assessed as "moderate risk," and scores of less than 4 were assessed as "high risk." The study quality assessment was independently performed by 2 reviewers, and the inconsistencies were resolved by consensus.

Data Synthesis and Analysis

We conducted meta-analyses on HRs and 95% CIs for RFS, PFS, and CSS using Stata software (version 11.0).

Heterogeneity and Publication Bias

The Cochrane *Q* test was used to evaluate statistical heterogeneity ($p < 0.10$). The I^2 statistic was used to assess the contribution of between-study heterogeneity to overall heterogeneity [6]. To evaluate publication bias, Begg's and Egger's tests were performed. Meta-regression was used to analyze the heterogeneity.

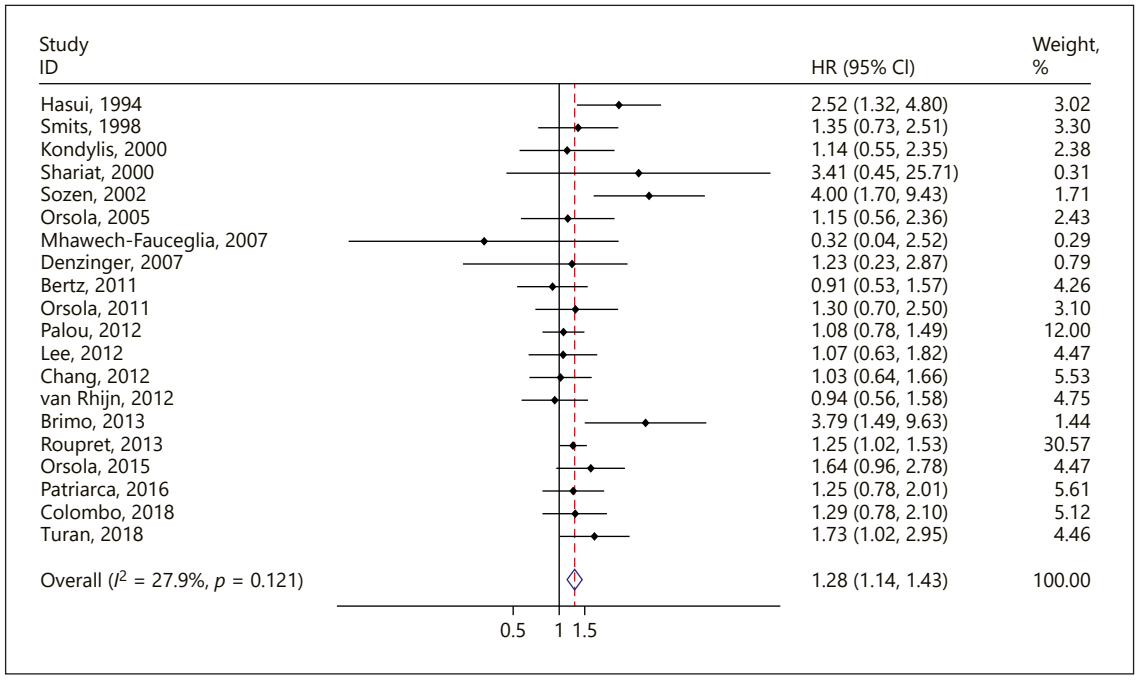

Fig. 2. T1a/b sub-staging: RFS. Difference in RFS between T1a and T1b sub-staging. RFS, recurrence-free survival.

Results

900 potentially relevant articles were initially included after database searches. The study flow chart is presented in Figure 1. We selected 68 articles for full-text review, of which 35 studies met the inclusion criteria. For each study, the data were extracted (online suppl. Table 2). Five studies were performed in Asia [7–11], 20 were performed in Europe [1, 12–30], and 10 were performed in North America [31–40]. RFS was evaluated in 20 studies, PFS was evaluated in 31 studies, and CSS was evaluated in 12 studies. Median follow-up time ranged from 12 to 114 months, with a median of 57.3 months. The 35 studies included 100% of patients with T1 BC.

The difference was found in RFS between T1a and T1b sub-stage (HR 1.28, 95% CI 1.14–1.43, $p < 0.001$) (Fig. 2). The significant difference was observed in PFS between the 2 arms (HR 2.18, 95% CI 1.95–2.44, $p < 0.001$) (Fig. 3), and T1b patients had worse CSS than T1a patients (HR 1.36, 95% CI 1.21–1.54, $p < 0.001$) (Fig. 4).

The risk of bias was calculated to be low or moderate for included studies. Thirty-three studies were rated low-risk of bias and 2 were moderate-risk. The scale scores are conveyed in online suppl. Table 3. We did not find any heterogeneity among studies by evaluating the RFS (I^2 = 27.9%). Significant heterogeneity was observed for PFS and CSS (I^2 = 60.7%, I^2 = 67.0%). Begg's funnel plots did not reveal any statistically significant publication bias in studies (that evaluated RFS [p = 0.230] and CSS [p = 0.837]) (Fig. 5a, b). The results derived from Egger's test were also consistent with abovementioned results (p = 0.236 and p = 0.335). When evaluating PFS, statistically significant publication bias was identified by Begg's funnel (p = 0.002) (Fig. 5c) and Egger's test (p = 0.087).

Discussion

The current classification recommends the reporting of the extent of invasion of T1 BCs. However, the system for sub-staging to be used remains optional. T1 sub-stage based on MM invasion was identified as an important prognostic factor for T1 BC. The T1 sub-staging system may help categorize patients into different subgroups with different clinical outcomes. The typical symptom of MM invasion is the change of MM distribution pattern from a continuous layer to a dispersed smooth muscle cell bundle. It was reported that the presence of MM could be found only in 32% of TURBT specimens and 17% of biopsy specimens [41–45]. In some areas of the bladder,

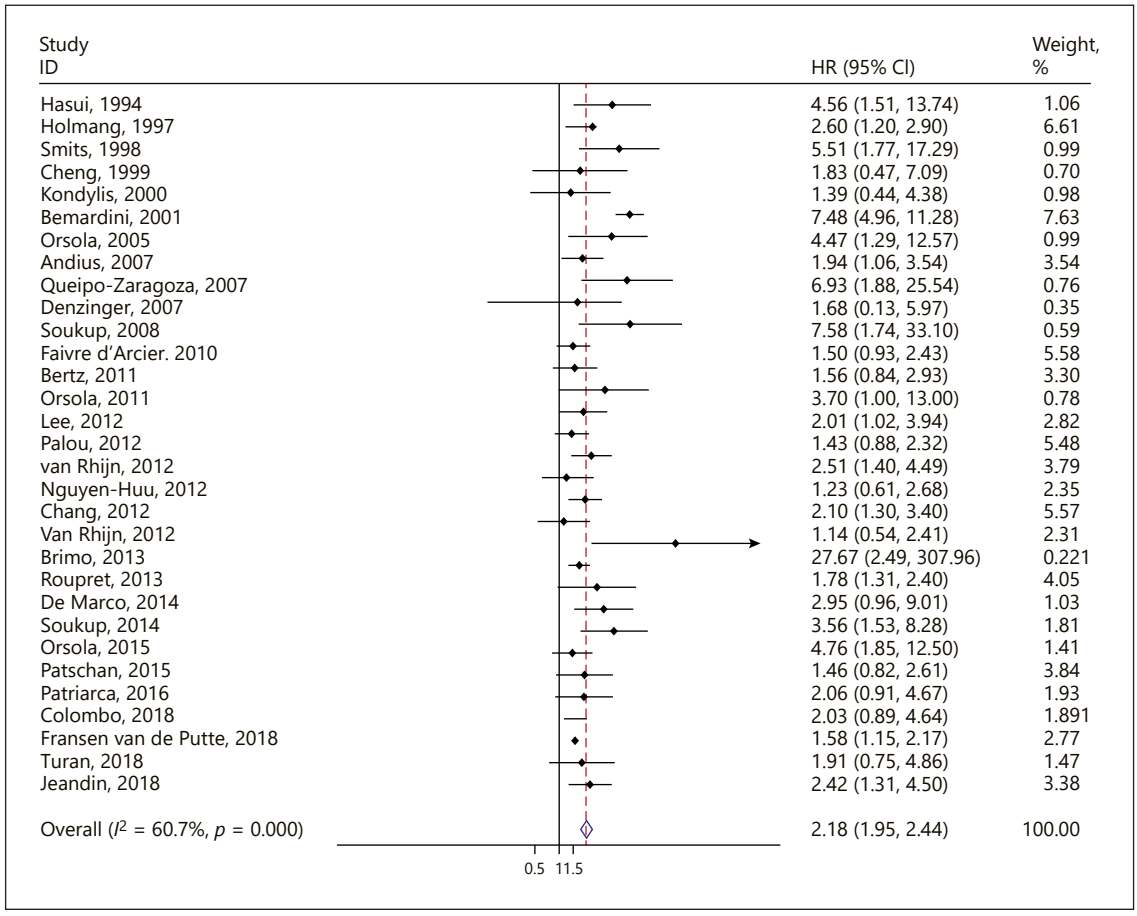

Fig. 3. T1a/b sub-staging: PFS. Difference in PFS between T1a and T1b sub-staging. PFS, progression-free survival.

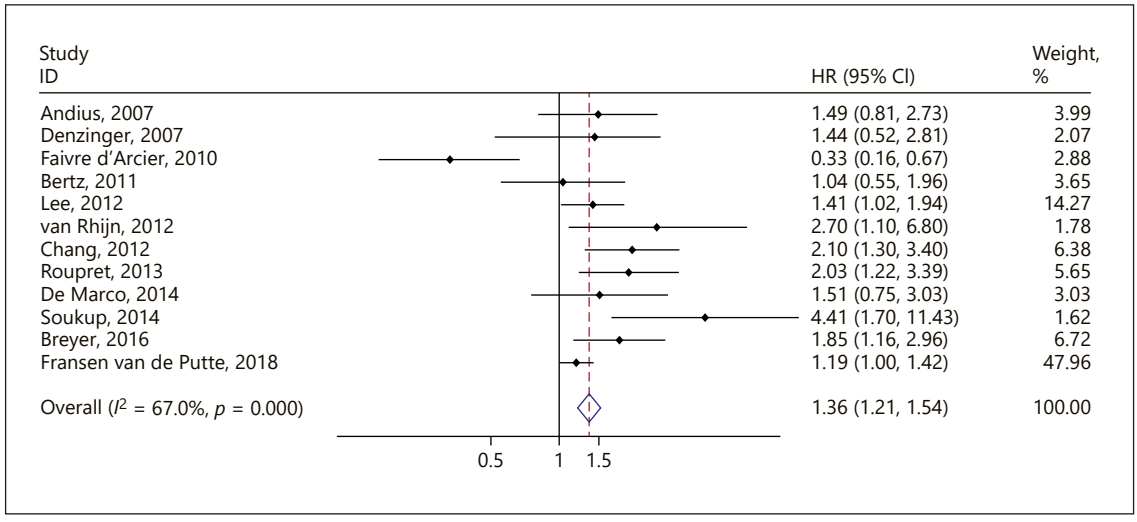

Fig. 4. T1a/b sub-staging: CSS. Difference in CSS between T1a and T1b sub-staging. CSS, cancer-special survival.

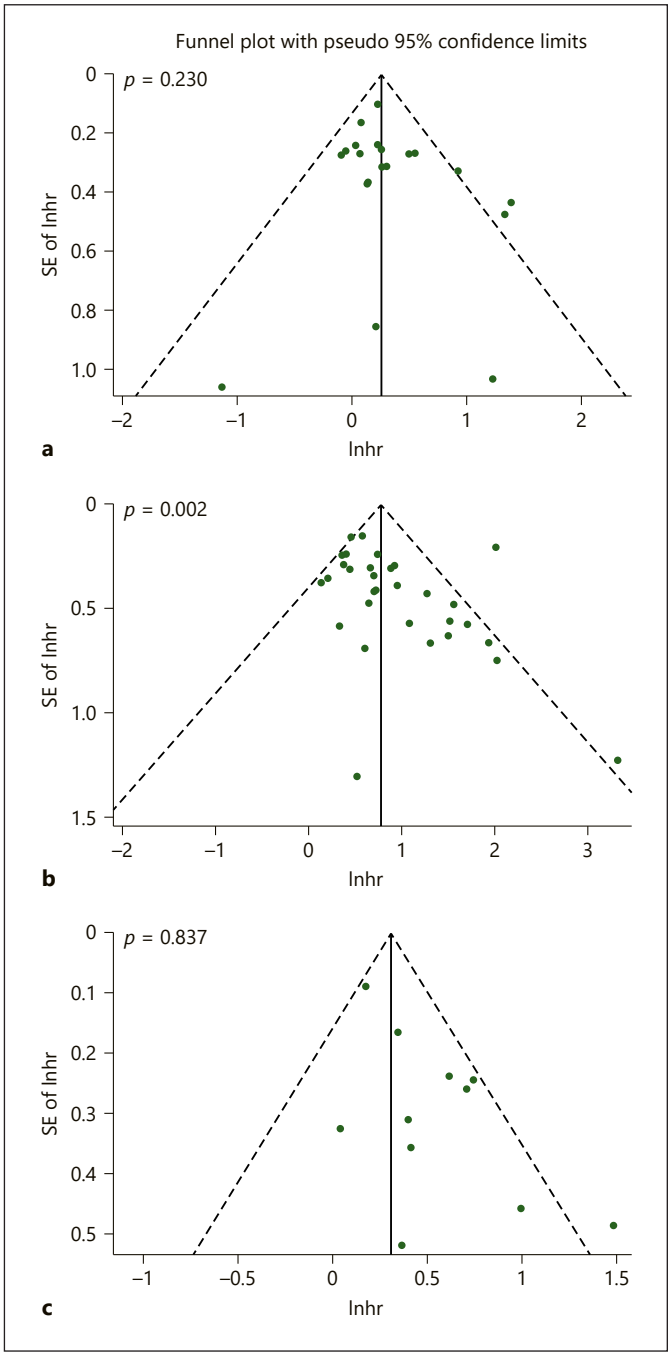

Fig. 5. Publication bias assessment: funnel plots. RFS (**a**); PFS (**b**); CSS (**c**). RFS, recurrence-free survival; PFS, progression-free survival; CSS, cancer-special survival.

such as trigone, the MM may be difficult to be identified [46], while the rate of MM discovery has increased up to 100% in more recent reports now. Most of them agreed on a 90% discovery rate [12]. It is important for urologists and pathologists to work together to identify the MM invasion. First, the urologists need to minimize the cautery injury when performing TURBT and submit the tumor base separately. These will enable the pathologist to have a better opportunity to identify the MM invasion depth. En-bloc resection using monopolar or bipolar current, Thulium-YAG, or Holmium-YAG laser is proven to be feasible. It provides resected specimens of high quality with detrusor muscle preserved [47, 48]. Second, well-trained pathologists need to sub-stage the tumor in most patients with stage T1 BC.

Martin-Doyle et al. [2] previously conducted a meta-analysis in comparing the recurrence rate between T1a and T1b/c high-grade BC based on 6 studies published before 2015. They found that T1a high-grade BC patients had no difference in recurrence compared with T1b/c high-grade BC patients (HR 1.29, 95% CI 0.93–1.78, $p = 0.127$). We evaluated 20 studies including both T1 low-grade BC and T1 high-grade BC. We found the difference in recurrence between T1a BC and T1b BC patients (HR 1.28; 95% CI 1.14–1.43, $p < 0.001$). The different clinical outcomes in our study were explained as follows. First, the population in our study covered all types of T1 BC, rather than T1 high-grade BC. Second, most studies focused on progression rate, with fewer studies reporting the recurrence of BC. Third, the invasion of MM was more frequently discovered.

We analyzed the heterogeneity in studies, which evaluated RFS and CSS with meta-regression. As individual patient data were not accessible, the assessment of heterogeneity was limited. We only analyzed the factors of publication year and race using covariate meta-regression, respectively. We found the publication year was related to the heterogeneity in studies which evaluated PFS ($p = 0.014$), while the race was not related to the heterogeneity ($p = 0.822$). We found that neither publication year ($p = 0.538$) nor race ($p = 0.705$) was related to the heterogeneity in studies which evaluated CSS. Although we identified little evidence of publication bias, we might have limited capabilities to detect the bias, given the limitations of available techniques [49]. This publication bias might be originated from selective reporting of results.

The treatment of T1 BC remains controversial. For patients receiving no adjuvant intravesical treatment, the progression rate was 9.1% in patients with T1a tumor, whereas it was 50% in patients with T1b tumor [8]. Orsola et al. [12] reported that in BCG-treated patients, the progression rate was 8% in patients with T1a tumor, whereas it was 34% in patients with T1b tumor. Overall, the progression rate of T1b patients was higher than that

of T1a patients. In our study, T1b patients had worse RFS, PFS, and CSS than T1a patients. So, patients with T1a tumor could be managed conservatively with TURBT and intravesical BCG treatment. But patients with T1b tumor should be recommended to receive more aggressive treatment such as early cystectomy.

There were some limitations in our study. First, all included studies were retrospective observational studies with selection biases. Second, insufficient data which lacked details on the presence of carcinoma in situ and employment of whether re-TURBT or intravesical treatment limited further analyses. Third, this study did not distinguish between low-grade and high-grade cancers, which might also influence disease recurrence and progression.

From our meta-analysis, we confirmed that T1b staging based on MM invasion could be a significant and adverse prognostic factor for RFS, PFS, and CSS of patients with T1 BC. Therefore, urologists and pathologists should be encouraged to work together to evaluate MM invasion, and T1 sub-staging system based on MM invasion should be recognized as a routine part of any histopathological report when possible. Future research works such as multicenter randomized clinical trials should be conducted to confirm our opinions.

Statement of Ethics

This is a meta-analysis and for this type of study, a statement of ethics is not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.F.: conceptualization, methodology, investigation, data curation, analysis, resources, visualization, supervision, and project administration. G.C.: conceptualization, methodology, investigation, data curation, formal analysis, resources, and writing – original draft and visualization. T.Y.: investigation, formal analysis, and writing – review. M.Z. and Q.S.: investigation, data curation, and writing – review and editing. B.Y. and P.Z.: data curation, visualization, and editing.

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