Prognostic value of the 8th edition of the tumor-node-metastasis classification for patients with papillary thyroid carcinoma: a single-institution study at a high-volume center in Japan

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Abstract. The tumor-node-metastasis (TNM) staging system is most commonly adopted to evaluate the prognosis of patients with thyroid carcinoma. The 8th edition of the TNM staging system, an extensively revised version of the 7th edition, was recently released. We aimed to investigate whether and how well the 8th edition reflects the cause-specific survival (CSS) of patients with papillary thyroid carcinoma by analyzing the cases in 5,892 patients who underwent initial surgery at Kuma Hospital between 1987 and 2005. The median postoperative follow-up duration was 178 months (range: 6–357 months). One patient with T4b disease was excluded from the analysis. Overall, 116 (2.0%) patients died of thyroid carcinoma. The proportion of variance explained (PVE) for CSS in the 7th and 8th editions was 10.69 and 10.97, respectively. Using the 7th edition, CSS of patients with stage IV A and stage III disease was similar (p = 0.32). In contrast, using the 8th edition, CSS was poorer in stage II than in stage I (p < 0.001), in stage III than in stage II (p < 0.001), and in stage IVB than in stage III (p < 0.001). Similar results were observed for disease-free survival. Although we could not establish any objective evidence that the 8th edition is superior to the 7th edition, the 8th edition is simpler and more convenient, as it includes fewer stages and addresses the issue of the 7th edition where stage IV A and III patients had similar prognoses.

Key words: Papillary carcinoma, Thyroid, Tumor-node-metastasis staging system, Lymph node metastasis, Carcinoma extension

PAPILLARY THYROID CARCINOMA (PTC) generally follows an indolent course. However, when associated with certain clinicopathologic features, PTC can be aggressive and is associated with a dismal prognosis. Thus, accurate evaluation is important for deciding on appropriate surgical therapy and postoperative follow-up of patients with PTC.

Of the several classification systems used for prognostication in PTC, the tumor-node-metastasis (TNM) staging system is used most widely. This system includes age, tumor size and extrathyroid extension (T factor), lymph node metastasis (N factor), and distant metastasis (M factor). The revised 8th edition of the TNM staging system (TNM–8th) was released in late 2016 [1]; some important changes have been made compared with the 7th edition (TNM–7th) [2]. Specifically, the age cutoff increased from 45 to 55 years and the significance of the T and N factors changed. Other important changes include the following: Evaluation of the T factor is based not only on preoperative physical examination, endoscopy, and imaging (as it was in the TNM–7th) but also on intraoperative gross findings. In the TNM–7th, two types of extensions were adopted, minimal and significant extension. Tumors with minimal extension were
upgraded to T3 if they were smaller than 4 cm. The
TNM–8th does not adopt upgrading by minimal exten-
sion, and has significant extension classified into three
categories, namely T3b, T4a, and T4b. The definition of
T4b has not changed from that in the TNM–7th. How-
ever, significant extension to strap muscles, which was
classified as T4a in the TNM–7th, is now downgraded to
T3b. Moreover, the TNM–8th notes that any data
obtained in the first 4 months of follow-up after surgery
should be used to define the prognostic stage. Therefore,
carcinoma with distant metastasis detected by radioactive
iodine (RAI) adjuvant therapy after surgery, even though
not detected by preoperative imaging studies, is classi-
fied as M1. In the 8th edition, findings obtained up to 4 months after surgery are included in the TNM staging system.

Table 1  List of changes from the TNM–7th staging system to the TNM–8th staging system

| Change                                                                 | Description                                                                 |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------|
| The cutoff age at diagnosis for staging was raised from 45 to 55 years. |
| The criteria for diagnosing extrathyroid extension were changed from pre-operative findings to gross findings based on intra-operative findings. |
| Minor extrathyroid extension was removed from T3.                     |
| T3a, a new category, indicates a tumor > 4 cm in the greatest dimension with no gross extrathyroid extension. |
| T3b, a new category, indicates a tumor of any size with gross extrathyroid extension invading only the strap muscles (in the anterior direction). |
| T4a indicates gross extrathyroid extension invading the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve. |
| Patients having upper mediastinal lymph nodes are classified as having N1a disease (N1b disease in TNM–7th). |
| In the 8th edition, findings obtained up to 4 months after surgery are included in the TNM staging system. |

Table 2  Stages based on the TNM–8th staging system

| Stage | Description                                                                 |
|-------|-----------------------------------------------------------------------------|
| Stage I | All M0 patients younger than 55 years and patients aged 55 or older with T1 and T2 tumors (≤4 cm) if N0/Nx M0. |
| Stage II | All M1 patients younger than 55 years and patients aged 55 or older with T1 or T2 tumors with N1M0, or T3a/T3b tumors with any NM0. |
| Stage III | Patients aged 55 years or older with T4a tumors with any N and M0. |
| Stage IV | Patients aged 55 years or older with T4b tumors with any N and any M and M1 with any T and any N. |

In this study, we aimed to investigate whether the changes made to the TNM–8th staging system are appro-
priate compared with the TNM–7th staging system for patients with PTC.

Materials and Methods

Patients

Between 1987 and 2005, a total of 5,892 patients underwent initial surgical treatment for PTC at Kuma Hospital; they were enrolled in this study. None of these patients had prior exposure to radiation therapy; none of the tumors demonstrated anaplastic transformation or coexisted with other thyroid malignancies, such as follicular carcinoma, medullary carcinoma, and malignant lymphoma; and none of these patients had a follow-up duration of less than 6 months. One patient with T4b tumor staged as IVB (TNM–7th) and IVA (TNM–8th) was excluded from our series. Our Institutional Review Board decided that this retrospective study did not need its approval.
**Diagnosis of PTC and preoperative evaluation**

All patients underwent ultrasonographic examination to evaluate the size and location of the primary lesion and metastatic lymph nodes, if present. The diagnosis of PTC was confirmed by histologic examination of ultrasound- or palpation-guided fine-needle aspiration biopsy (FNAB) specimens. The ultrasonographic diagnosis of lymph node metastasis was based on the criteria proposed by Antonelli et al. [3], except for lymph nodes > 1 cm in size, which were diagnosed as metastasis only when they fulfilled other criteria. FNAB of suspicious lymph nodes and thyroglobulin measurement of the wash-out from the needles used for FNAB [4] were performed if necessary to confirm the diagnosis and to decide whether the patient required therapeutic modified radical neck dissection. Lung and mediastinal lymph node metastasis was evaluated by means of preoperative imaging, such as computed tomography (CT) and thallium scintigraphy. During the study period, laryngoscopy was mainly performed for patients with hoarseness or whose PTC was located along the anatomic course of the recurrent laryngeal nerve; however, laryngoscopy has subsequently become routine practice.

**Intraoperative findings**

Intraoperatively, we grossly evaluated carcinoma extension from the thyroid gland and metastatic lymph nodes to adjacent organs. Cases that required at least partial excision of adjacent organs were categorized as being positive for carcinoma extension.

**Surgical procedures**

Thyroidectomy and (at least) ipsilateral central cervical lymph node dissection was almost routinely performed. Complete central cervical lymph node dissection was performed in patients who underwent subtotal, near total, or total thyroidectomy. Routine modified radical neck dissection was performed—either therapeutically or prophylactically—until 2007; this is described further in the Results section.

**Postoperative follow-up and evaluation of recurrence**

The postoperative treatments provided during the study period were significantly different from what is currently provided. In our series, only 82 patients underwent RAI ablation therapy using a dose of 30 mCi or more. Because the use of RAI was significantly restricted at that time, we adopted a strategy of performing RAI scintigraphy, using low doses of RAI (3–13 mCi), to detect distant metastases; this investigation was performed for 1,009 patients, 19 of whom underwent subsequent RAI ablation therapy.

The median postoperative follow-up period was 178 months (range: 6–357 months). The follow-up period after undergoing initial surgery extended to 10, 15, and 20 years for 4,910 (83%), 2,896 (49%), and 1,377 (23%) patients, respectively. We performed follow-up ultrasonography at least once per year to determine whether local recurrence had occurred. An annual chest radiography or CT scan was also obtained. Recurrence was defined as the presence of new lesions demonstrated on imaging studies. For patients who underwent total thyroidectomy, we followed the change in serum thyroglobulin levels by performing serial measurements thereof. Systemic investigation for distant recurrence, using CT and/or positron emission tomography-CT, was performed for patients demonstrating a short thyroglobulin doubling-time with rapid increases in the serum levels of thyroglobulin [5]. Regardless of thyroglobulin levels, we often performed such constant systemic investigations in aggressive cases with high-risk features such as extensive lymph node metastasis and severe gross extrathyroid extension, or those diagnosed as histologically aggressive due to the presence of poorly differentiated components and tall cell variant.

To investigate the cause-specific survival (CSS) of patients who no longer attended regular follow-up at our hospital, we sent repeated questionnaires to these patients and their families once a year.

**Statistical analysis**

The Kaplan-Meier method and log-rank test were adopted to analyze time-dependent variables. These analyses were performed using StatFlex (Artec, Co. Ltd., Osaka, Japan). A $p$-value < 0.05 was regarded as significant. Proportion of variance explained (PVE) was calculated by the Schemper-Henderson Predictive Measure in SAS software Ver 9.4 (SAS institute, Cary, North Carolina, USA).

**Results**

**Clinicopathologic features, surgical strategies, and prognosis**

Table 3 shows the clinicopathologic features of the 5,892 study participants. During the study period, in our hospital, similar to in many other Japanese institutions,
prophylactic modified radical neck dissection was commonly performed. In our series, 4,462 (75.7%) patients (3,909 + 553) (see Table 3, Extent of lymph node dissection) underwent at least unilateral modified radical neck dissection; 3,369 (76%) of these procedures were prophylactic. In contrast, total thyroidectomy was performed only for patients regarded by the attending physicians as having aggressive tumors, with features such as large tumor size, extrathyroid extension, bilateral tumors, and extensive lymph node metastasis. Thus, only 3,041 (52%) patients underwent total or near total thyroidectomy.

Distant metastasis was identified by preoperative imaging tests or postoperative RAI scintigraphy in 68 (1.2%) tumors classified as M1. As indicated in the Introduction, interpretation of M1 based on the TNM–7th is unclear and not uniformly applied; however, in this study, we classified patients as having M1 disease if metastases were detected not only by preoperative imaging tests but also by postoperative RAI scintigraphy or adjuvant RAI therapy, regardless of whether the TNM–7th or TNM–8th was used. Fifty of these patients received RAI therapy using at least 100 mCi; the other 18 did not, either because of poor-risk status or treatment refusal. To date, 659 patients (11.0%) have experienced recurrence of thyroid carcinoma. Local recurrence was demonstrated in 604 (10.3%) patients; sites of recurrence included the regional lymph nodes and the remnant thyroid. Distant recurrence—to the lungs, bone, and brain—was detected in 143 (2.4%) patients; 88 (1.5%) patients showed both local and distant recurrence, and 116 (2.0%) died of thyroid carcinoma.

Number of patients classified into stages based on the TNM–7th and TNM–8th staging systems

Table 4 shows the number of patients with each stage based on the TNM–7th and the TNM–8th staging systems. Stage I tumors in 3 and 54 patients aged 55 or older were upstaged to stage II and III, respectively, because of the presence of extrathyroid extension corresponding to T3b and T4a based on intraoperative findings. Of 867 tumors staged as II on the TNM–7th, 733 were down-staged to stage I on the TNM–8th, because their tumor sizes were less than 4 cm (range: 2.1–4.0 cm) or the patients were younger than 55 years of age. Another 99 were upstaged to stage III on the TNM–8th because of the presence of significant extrathyroid extension corresponding to T4a according to intraoperative findings. Among 279 stage III tumors on the TNM–7th, 108 were down-staged to stage I on the TNM–8th because of young age and 113 were down-staged to stage II due to the down-staging of tumors larger than 4 cm and N1a. All Stage IVA tumors

Table 3 Clinicopathologic characteristics of the 5,892 patients with papillary thyroid carcinoma enrolled in this study

| Variable                        | Category     | n  (%) |
|---------------------------------|--------------|-------|
| Sex                             | Male         | 657 (11) |
|                                 | Female       | 5,235 (89) |
| Age (years)                     | <45          | 1,927 (33) |
|                                 | 45–54        | 1,656 (28) |
|                                 | ≥55          | 2,309 (39) |
| Tumor size (cm)                 | ≤2.0         | 3,390 (58) |
|                                 | 2.1–4.0      | 1,908 (32) |
|                                 | >4.0         | 594 (10) |
| Extent of thyroidectomy         | Total or near total | 3,041 (52) |
|                                 | Subtotal     | 536 (9) |
|                                 | Limited thyroidectomy | 2,315 (39) |
| Extent of lymph node dissection | Not done     | 278 (5) |
|                                 | Central compartment only a | 1,152 (20) |
|                                 | Unilateral MND b | 3,909 (66) |
|                                 | Bilateral MND c | 553 (9) |
| Significant extrathyroid extension on preoperative evaluation | No | 5,723 (97) |
|                                 | Yes d        | 169 (3) |
| Significant extrathyroid extension on intraoperative evaluation | No | 5,111 (87) |
|                                 | Yes          | 781 (13) |
| N status                        | N0           | 4,654 (79) |
|                                 | N1a          | 145 (2) |
|                                 | N1b          | 1,093 (19) |
| Distant metastasis at surgery (M status) | No | 5,825 (99) |
|                                 | Yes          | 67 (1) |

MND, modified radical neck dissection

a One patient, b ten patients, and c two patients also underwent mediastinal compartment dissection, respectively. d Thirty-eight patients had anterior extension only (corresponding to T3b).
were down-staged, because of young age (to stage I) and the downgrading of N1b (to stage II) and significant extrathyroid extension (to stage II or III). Nine of 38 stage IVC tumors based on the TNM–7th were down-staged to stage II on the TNM–8th, because the patients were younger than 55 years of age.

**Disease-free survival in patients based on the TNM–7th and the TNM–8th staging systems**

We then investigated the disease-free survival (DFS) of M0 patients (n = 5,825) in each stage based on the TNM–7th and the TNM–8th. Table 5 shows the 10-, 15-, and 20-year DFS rates of patients in each stage based on 7th and 8th TNM staging systems. As shown in Fig. 1, based on the TNM–7th, stage II patients showed a poorer DFS than stage I patients, and stage III patients were significantly more likely to show recurrence than stage II patients (p < 0.001), but the DFS of stage III and IVA patients was not significantly different (p = 0.16). In contrast, the DFS of patients staged based on the TNM–8th became significantly poorer from stage I to III (p < 0.001) (Fig. 2). As shown in Table 5, the PVE values for DFS of TNM–7th and TNM–8th were 4.89 and 5.57, respectively.

**CSS of patients based on the TNM–7th and TNM–8th staging systems**

Figs. 3 and 4 show the CSS of patients based on the

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**Table 4** Number of patients in each stage in the TNM–7th staging system and their corresponding stages in the TNM–8th staging system

| TNM–7th | TNM–8th |
|---------|---------|
| I (n = 3,975) | 3,918  |
| II (n = 867) | 733    |
| III (n = 279) | 108   |
| IVA (n = 733) | 275   |
| IVC (n = 38) | 0      |

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Fig. 1 Kaplan-Meier graph showing the disease-specific survival (DFS) of patients with stage I, II, III, and IVA papillary thyroid carcinoma based on the 7th edition of the TNM staging system.

Stage I vs. II: p < 0.001; stage II vs. III: p < 0.001; stage III vs. IVA: p = 0.16
TNM–7th and TNM–8th staging systems. The 10-, 15-, and 20-year CSS rates of patients in each stage according to these two editions of the TNM system are shown in Table 6. As described in the Materials and Methods section, our cohort did not include T4b cases, and there were no stage IVB (TNM–7th) or IVA (TNM–8th) tumors. Applying the TNM–7th system, CSS worsened with increasing stage (p < 0.001 for stage I vs. II, and p < 0.001 for stage II vs. III), but CSS did not differ between patients with stage IVA and stage III disease (p = 0.32; Fig. 3). When applying the TNM–8th system, CSS was less favorable for patients with stage II than with stage I disease (p < 0.001), and for patients with stage III than with stage II disease (p < 0.001). PVE for CSS of the TNM–7th and TNM–8th were 10.69 and 10.97, respectively (Table 6).

**Discussion**

In this study, we investigated whether and how well...
the TNM staging system reflects the CSS of patients with PTC. We objectively compared the TNM–8th and TNM–7th based on PVE. As shown in Table 5, the PVE for DFS of the TNM–8th was higher than that of the TNM–7th, but the PVE for CSS was similar between the two editions (Table 6). This similarity may be explained by the small number of patients who died of PTC, and thus, we could not objectively show that the TNM–8th is significantly better than the TNM–7th, at least for CSS. However, there are four stages in the TNM–7th (stage I to IVA) for M0 patients (except for older T4b patients who may be stage IVB), and the CSS was very similar between stage III and IVA. In contrast, in the TNM–8th, the same series of patients were divided into only three stages, each with clearly differing CSS rates. Similar findings were also observed for the DFS of patients.

**Table 6** Cause-specific survival rates according to the 7th and 8th editions of the TNM staging system in this cohort

| Staging system | Stage | 10-year CSS rate (%) | 15-year CSS rate (%) | 20-year CSS rate (%) | PVE |
|----------------|-------|----------------------|----------------------|----------------------|-----|
| 7th edition TNM | I (n = 3,975) | 100 | 99.8 | 98.7 | |
| | II (n = 867) | 99.4 | 97.8 | 97.5 | |
| | III (n = 279) | 96.5 | 94.1 | 91.9 | 10.69 |
| | IVA (n = 733) | 95.0 | 92.2 | 88.8 | |
| | IVC (n = 38) | 46.5 | 37.5 | 25.1 | |
| 8th edition TNM | I (n = 5,034) | 99.8 | 99.6 | 99.3 | |
| | II (n = 408) | 96.3 | 94.9 | 93.2 | 10.97 |
| | III (n = 421) | 92.1 | 86.5 | 82.7 | |
| | IVB (n = 29) | 33.5 | 20.1 | 10.0 | |

CSS, cause-specific survival
PVE, proportion of variance explained

**Fig. 3** Kaplan-Meier graph showing the cause-specific survival (CSS) of patients with stage I, II, III, IVA, and IVC papillary thyroid carcinoma based on the 7th edition of the TNM staging system.

Stage I vs. II: p < 0.001; stage II vs. III: p < 0.001; stage III vs. IVA: p = 0.32; stage IVA vs. IVC: p < 0.001
Therefore, although we could not establish any objective evidence that the TNM–8th is superior to the TNM–7th, TNM–8th is simpler and more convenient to use.

The TNM–8th staging system contains some significant differences compared with its predecessor. Most importantly, the age cutoff changed from 45 to 55 years. Previous studies have proposed various age cutoffs, such as 50, 55, and 60 years [3, 6-13]. Some studies showed that 55 years is a better cutoff age than 45 years in terms of accurately predicting prognosis [6, 12, 13]. In the TNM–8th, tumors > 4 cm in the longest diameter in patients aged ≥ 55 years were downgraded from stage III to stage II, tumors 2.1–4.0 cm in the longest diameter were downgraded from stage II to stage I, N1 tumors were downgraded from stages IVA or III to stage II, and tumors showing significant extension were downgraded from stage IVA to stage III or stage II (if extension is only to the strap muscles).

The TNM–7th staging system adopted extrathyroid extension based only on preoperative findings. However, extrathyroid extension is difficult to diagnose on imaging studies, unless there is recurrent laryngeal nerve paralysis due to dorsal extension of the tumor or tumor protrusion into the trachea and/or esophagus; the latter may be detected by CT, magnetic resonance imaging, esophagoscopy, or bronchoscopy. Therefore, in our series, only 169 (3%) patients were diagnosed as having extrathyroid extension preoperatively. After including intraoperative gross extrathyroid extension, the number of patients with extrathyroid extension increased to 781 (13.3%). This resulted in the increased number of patients with stage III disease when classified using the TNM–8th.

The TNM staging system does not adopt the range and depth of significant extrathyroid extension. Sugitani et al. demonstrated that the prognosis of patients having extension to the recurrent laryngeal nerve changed with the presence or absence of preoperative recurrent laryngeal nerve paralysis [14], although these results were not confirmed in another study [15]. Nishida et al. showed that the prognosis of patients having tracheal invasion varied with the depth of invasion, e.g., cartilage only or tracheal mucosa [16]. Hotomi et al. demonstrated that the prognosis of patients with papillary thyroid carcinoma was dependent on the organs invaded by the carcinoma [17]. Therefore, it is logical to conclude that the prognosis of patients with significant extension to adjacent organs differs based on which organs have been invaded by the carcinoma and to what depth. Adopting this factor may further improve the usefulness of the TNM staging system.

One may think that extrathyroid extension based on postoperative pathologic examination is more accurate. However, invasion to adjacent organs such as the muscular layer of the esophagus and the recurrent laryngeal

Fig. 4 Kaplan-Meier graph showing the cause-specific survival (CSS) of patients with stage I, II, III, and IVB papillary thyroid carcinoma based on the 8th edition of the TNM staging system.

Stage I vs. II: $p < 0.001$; stage II vs. III: $p < 0.001$; stage III vs. IVB: $p < 0.001$. 

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nerve is difficult to evaluate even if these tissues are resected with the tumor. Pathologic invasion is confirmed only when invasion is visible on microscopy; if not apparent, pathologists diagnose the specimens as being negative for invasion. Importantly, this method does not accurately reflect the biologic characteristics of PTC. Indeed, the MACIS score [18] includes extrathyroid invasion visible with the naked eye.

Kim TH et al. [19] and Kim M et al. [20] investigated a similar issue—both demonstrated that the TNM–8th predicted the CSS of patients with differentiated thyroid carcinomas more accurately than the TNM–7th. Oddly, the proportion of patients with stage III disease was very low in these studies. In the case series of Kim TH et al. [19], only 2.3% of patients were classified by the TNM–8th as having stage III disease, a significantly smaller proportion than that in our series (6.9%). Kim M et al. [20] showed that only 30 of 1,613 tumors (1.8%) were classified into stage III using the TNM–8th. Moreover, in their series, none of the tumors were upgraded from stage I or II to stage III, although a significant number of tumors were up-staged to stage III in our series, which is due to the presence of extrathyroid extension based on intraoperative findings. The discrepancies between the findings in those studies and ours may be explained by differences in the method of assessing gross extrathyroid extension among these studies.

Another important change is in the evaluation of the N factor. Indeed, the prognosis of N1 patients is poorer than that of N0 patients, but in the TNM–7th, all N1a patients and N1b patients aged 45 or older were classified as having stage III and stage IVA, respectively. However, we demonstrated that the prognosis of N1b patients was not different from that of N1a patients [21]. Moreover, PTC with a high N has an aggressive character and a poor prognosis [14, 22], but the prognostic impact of low N in most N-positive patients was not large [22]. These indicate the appropriateness of N1 tumors being down-staged to stage II, despite the patients being 55 years or older.

Our study has some limitations. It was a retrospective study and enrolled patients received different therapies from those currently in use. During the study period, the incidence of total thyroidectomy was lower than it is at present, indicating that patients with high-risk features such as large size, clinically apparent lymph node metastasis, and significant extrathyroid extension did not always undergo total thyroidectomy. Instead, prophylactic modified radical neck dissection was performed, even for patients without any high-risk features; this strategy has subsequently been shown not to improve prognosis [23]. Because of the strict limitations pertaining to RAI administration, many patients underwent RAI scintigraphy rather than RAI ablation therapy. It is unclear whether this affected prognosis. Nonetheless, this should be regarded as a limitation of this study. A further limitation is the absence of participants with stage IVB and stage IVA tumors according to the 7th and 8th TNM editions, respectively. The difference in prognosis between these patients and those with other stages of disease needs to be elucidated.

In this study, we could not demonstrate the objective superiority of the TNM–8th over the TNM–7th for evaluating the CSS of patients, because the PVEs were similar between the two editions. However, the TNM–8th eliminated the complication in which the DFS and CSS of stage III and IVA in the TNM–7th were similar. Furthermore, the number of stages for M0 patients was decreased in the TNM–8th, making it simpler and more convenient to evaluate the prognosis of patients with PTC.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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