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Clinical characteristics and treatment outcomes of patients with small cell carcinoma of the urinary bladder

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Abstract

Background: Small cell carcinoma of the urinary bladder (SCUB) is rare. The optimal treatment for SCUB remains unclear. To address the problem of appropriate treatment for each case, we assessed single-modality and surgery-based multimodality treatments in patients with SCUB.

Materials and methods: We retrospectively reviewed the medical records of 12 patients with SCUB between 1990 and 2013. All patients underwent transurethral resection of the bladder tumor and were diagnosed with SCUB. Their clinicopathological characteristics were assessed, and the outcomes were compared according to the treatment modality.

Results: The median (range) age at diagnosis was 66 years (range, 53–85 years). T1–4N0M0 was observed in 8 patients (66%), N1–3M0 in 2 (17%), and NanyM1 in 2 (17%). After transurethral resection of the bladder tumor, 6 patients (50%) underwent cystectomy alone, and 4 (33%) underwent cystectomy and presurgical or adjuvant chemotherapy with etoposide and cisplatin. During the median follow-up period of 20.7 months, 6 patients (50%) died of cancer, and 2 patients (17%) died of other causes. The median overall survival period was 1.9 years. The 5-year overall survival rate in patients who underwent cystectomy and chemotherapy was 75%, whereas that in those who underwent cystectomy alone and transurethral resection alone were 22% and 0%, respectively ($p = 0.012$). Recurrence-free survival was significantly correlated with cause-specific survival ($r = 0.95$; 95% confidence interval, 0.81–0.99; $p < 0.001$).

Conclusions: Radical cystectomy with chemotherapy using the etoposide and cisplatin regimen improved the prognosis of patients with SCUB and TxNxM0. The time from initial progression to death due to cancer was very short, indicating that the initial treatment strategy is crucial.

Keywords: Bladder cancer; Small cell carcinoma; Treatment; Chemotherapy; Radical cystectomy

1. Introduction

Small cell carcinoma of the urinary bladder (SCUB) is a rare cancer that accounts for less than 1% of all primary bladder cancers.[1] A recent report from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated that the incidence of SCUB increased significantly from 0.3% to 0.6% among all bladder malignancies from 1991 to 2005.[2] Small cell carcinoma of the urinary bladder has been shown to be an aggressive malignancy characterized by rapid progression and early metastases.[3,4] Almost half of the patients with SCUB have their disease diagnosed when it has already reached an advanced stage and consequently have poor survival.[2–4] The prognosis also worsens because standard treatments have not yet been established.

In general, multimodal approaches are needed for the optimal management of this aggressive disease.[2,5,6] Several large cohort studies have reported various treatment patterns for SCUB.[6] According to the National Cancer Database, 960 patients were diagnosed with SCUB with either nodal (TxN + M0, $n = 364$) or distant metastases (TxNxM1, $n = 596$) between 1998 and 2010.[6] Of these, 483 (50.3%) were treated with palliative therapy alone, 141 (14.7%) with single-modality treatment, 203 (21.1%) with surgery-based multimodal treatment, and 133 (13.9%) with radiation-based multimodal treatment. The SEER database indicates that the use of transurethral resection of bladder tumors (TURBTs) has increased significantly over the past 2 decades for all stages of the disease, whereas the use of all other treatment modalities has remained relatively stable.[2]

Considering the above, multimodal treatment is not always the mainstream management method for SCUB, which means that the standard treatment is still unclear. To address the problem of appropriate treatment for each case, we assessed single-modality and surgery-based multimodality treatments in Japanese patients with SCUB.

2. Materials and methods

We retrospectively reviewed the records of 12 patients with SCUB who were treated at our hospital between January 1990 and December 2013. All patients underwent TURBT and were diagnosed with SCUB by several pathologists at our hospital. Their clinicopathological characteristics, including age, sex, type of

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treatment, and cancer staging, were assessed according to the tumor, node, metastasis (TNM) staging TNM classification system.[3] Laboratory data were obtained, and computed tomography (CT) scans of the thorax and abdomen were performed for staging. Serum neuron-specific enolase and serum progastrin-releasing peptide levels were measured when the histological diagnosis of SCUB was established after TURBT. These examinations were performed every 3 or 6 months throughout the follow-up period. Brain CT scans were conducted when the patients were in an advanced stage or had neurological symptoms.

We have a policy to perform radical cystectomy with regional lymph node dissection in patients with SCUB without distant metastasis. Even when pathological T0 is diagnosed, adjuvant chemotherapy has been administered since 2006. If patients have clinical regional lymph node metastasis, radical cystectomy is performed for those responsive to presurgical chemotherapy. If patients have distant metastases, chemotherapy is administered after TURBT. Radical cystectomy with regional lymph node dissection and creation of an ileal conduit or orthotopic ileal neobladder was performed in 10 patients. Chemotherapy, including presurgical or adjuvant therapy, was administered to 5 patients. The main regimen was cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 (EP) on days 1–3, repeated for 3 weeks. One patient who had local recurrence and systemic metastasis after cystectomy was treated with a regimen of cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8, and 15, which was repeated after 4 weeks. The responses to systemic treatment were evaluated according to the Response Evaluation Criteria in Solid Tumors criteria version 1.1 on CT scans of the thorax and abdomen.

The time of clinical progression was defined as the time of the first occurrence of local recurrence, distant metastasis, or first progression of systemic metastatic lesions. Cause-specific survival (CSS) from diagnosis to death due to bladder cancer and overall survival (OS) from diagnosis to death due to bladder cancer or other causes were calculated. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to compare survival outcomes between different subgroups of patients. Spearman correlation coefficient (range, 0–1, 95% confidence interval [CI]) was used for the correlation analysis between recurrence-free survival and CSS. Statistical significance was set at a p value less than 0.05. All statistical analyses were performed using EZR for Windows (Saitama Medical Center; Jichi Medical University, Saitama, Japan).

3. Results

Patient characteristics are shown in Table 1. We included 9 male and 3 female patients. The median (range) age at diagnosis was 66 years (53–85 years). Stage I was observed in 1 patient, stage II in 6, stage III in 1, and stage IV in 4. Histologically, 3 patients had pure SCUB and 9 patients had a mixed type of SCUB and urothelial carcinoma (UC), adenocarcinoma (AC), or squamous cell carcinoma (SCC).

The profiles of all patients with SCUB are shown in Table 2. After TURBT, 6 patients underwent cystectomy alone, and 4 underwent cystectomy and presurgical or adjuvant chemotherapy. Of those who received chemotherapy, 3 patients (no. 7, 8, and 9) received 2 cycles of adjuvant EP, and 1 patient (no. 10) who had tumor invasion of the pelvic wall and bilateral obturator lymph node metastasis received 3 cycles of presurgical EP. Of the 2 patients who had systemic metastasis at diagnosis, one (no. 11) was determined to be unfit for chemotherapy due to their poor performance status, and the other (no. 12) received EP. However, the latter patient's systemic condition worsened with disease progression during one cycle of EP, and because their performance status worsened, they were unable to continue treatment.

Table 1

Characteristics of the patients with SCUB.

Characteristics	n = 12
Age at diagnosis, median (range), yr	65.5 (39–85)
Sex, n (%)	
Male	9 (75)
Female	3 (25)
ECOG PS, n (%)	
≤1	10 (83)
≥2	2 (17)
TNM stage, n (%)	
T1–2N0M0	7 (58)
T3–4N0M0	1 (8)
TanyN1–3M0	2 (17)
TanyN0M1	0
TanyN1–3M1	2 (17)
Metastases at diagnosis	
Regional lymph node	3 (25)
Liver	2 (17)
Others	2 (17)
Histology	
Pure SCUB	3 (25)
Mixed with	9 (75)
UC	4 (50)
UC and AC	2 (17)
UC, AC, and SCC	1 (8)

AC = adenocarcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status; SCC = squamous cell carcinoma; SCUB = Small cell carcinoma of urinary bladder; UC = urothelial carcinoma.

During the median follow-up period of 20.7 months, 6 patients (50%) died of cancer and 2 patients (17%) died of other causes. The median OS period was 22.8 months. The 5-year OS rate in patients with cystectomy and chemotherapy was 75%, whereas in those with cystectomy alone and with transurethral resection alone, the rates were 22% and 0%, respectively (p = 0.004; Fig. 1). There was no significant difference in the OS between SCUB only and SCUB mixed with other histologies, including UC, AC, and SCC (5-year OS rate: 33% vs. 40%, p = 0.719). Of the 6 patients who underwent cystectomy alone, 5 had systemic recurrence early after cystectomy. Two patients (no. 2 and 5) with locally advanced disease had brain metastases and received radiation treatment. One patient (no. 4) was initially diagnosed with UC and AC (not SCUB) and underwent radical cystectomy. However, 6 months later, they experienced local recurrence and multiple metastases in the lymph nodes, skin, muscle, and bone. After a skin lesion was diagnosed as small cell carcinoma, SCUB in bladder specimens was diagnosed by immunohistochemical pathological review. One patient (no. 9) had lung metastasis 7.5 years after cystectomy and 2 cycles of adjuvant EP chemotherapy. We conducted 4 cycles of EP and prophylactic cranial irradiation, totaling 25 Gy. Recurrence-free survival was significantly correlated with CSS (r = 0.95; 95% CI, 0.81–0.99), and the difference between the time to initial progression and survival time was small (Fig. 2).

4. Discussion

Here, we examined the appropriate treatment for SCUB based on the profiles of patients with SCUB. Patients with surgically resectable disease (pT1–4N0M0) and even nonadvanced stages of disease (pT0, pT1, or pT2) had poor outcomes with cystectomy alone

compared with cystectomy and adjuvant chemotherapy. When disease progression during presurgical chemotherapy is not observed in patients with lymph node metastasis, cystectomy can be considered a useful treatment modality. Our results suggest that cystectomy and chemotherapy should be considered for patients with SCUB without distant metastasis. In addition, 1 patient (no. 9) received prophylactic cranial irradiation and survived for a long time. Prophylactic cranial irradiation may be a consolidative option for a subset of patients with advanced SCUB.

Patients with SCUB have a higher rate of advanced stage disease than those with UC,[2] which can lead to different prognostic outcomes. Does this mean that SCUB is biologically aggressive? Kaushik et al.[7] reported outcomes for patients with SCUB who underwent cystectomy compared with those with pure UC. Although patients with SCUB received more adjuvant chemotherapy, the survival outcomes of SCUB seemed to be similar to those of UC when matched by TNM stage. A large cohort study showed that the outcomes of patients with SCUB were similar to those of patients with UC in a subset with distant metastases.[6] However, in a subset with only lymph node involvement (TanyNanyM0), SCUB was worse than UC.[6] Therefore, it is necessary to develop an appropriate treatment strategy for SCUB with aggressive features, particularly for SCUB without distant metastasis.

Cystectomy and radiation are modalities that should be considered for the local control of patients with SCUB. However, we often face a dilemma as to whether aggressive intervention for local control would be overtreatment and whether this would provide a significant clinical benefit for patients with SCUB stage T1 or lower. According to the SEER database study, T stage significantly affected OS, but the difference in T stage was small. Bladder preservation therapy, including TURBT alone and partial cystectomy, has been shown to be unfavorable because of high rates of recurrence and poor survival.[5,8,9] We found that even patients with pT0 or pT1 status in radical cystectomy had high rates of recurrence. Thus, bladder preservation therapy for SCUB is likely insufficient. Bladder preservation therapy may potentially reflect a lack of consensus regarding local control of mixed SCUB. In the present study, the histological findings indicated that the majority of patients had mixed SCUB plus UC. Likewise, in another series, the mixed type was observed in 35%–70% of cases and was most frequently accompanied by UC.[10,11] When bladder preservation therapy, including chemoradiation, was conducted for SCUB without distant metastases, there was a higher risk of local recurrence of mixed tumors compared with pure SCUB.[12]

Given the optimal treatment for SCUB, controlling the time to progression associated with survival, as seen in our study, can be an important issue. We demonstrated that patients who underwent radical cystectomy alone, even those with pT0 or pT1, had high rates of early recurrence, whereas those with 2 courses of adjuvant EP had no progression within 1 year after surgery. Similarly, Kaushik et al.[7] showed the potential benefit of adjuvant chemotherapy after radical cystectomy in 68 patients with SCUB. Although patients who received adjuvant chemotherapy had a higher rate of nodal metastases than those who did not receive adjuvant chemotherapy, they had significantly improved 5-year OS compared with those who did not (43% vs. 20%, $p = 0.03$). In addition, adjuvant chemotherapy was associated with a significantly decreased all-cause mortality (hazard ratio, 0.26, $p = 0.001$), regardless of the pT stage. These findings suggest that radical cystectomy alone may allow microscopic metastasis to develop over time. Thus, when radical cystectomy is conducted for SCUB without distant metastasis, adjuvant chemotherapy should be one of the treatment options to be considered, regardless of the pT stage in cystectomy.

Table 2

Profiles of the 12 patients with SCUB.

Patient	Age	Sex	ECOG PS	TNM	Metastases at diagnosis	Histology	Local treatment	pT stage	Chemotherapy	Initial progression	Time to initial progression, yr	Treatment approach for initial progression	Survival after diagnosis, yr
1	65	M	0	T2N0M0	-	SCUB, UC	RCx	pT1pN0	-	-	-	-	DOOD 14.2
2	71	M	1	T2N0M0	-	SCUB, UC	RCx	pT3bpN0	-	Lung, brain	0.6	Irradiation for brain	DOD 1.1
3	79	M	1	T2N0M0	-	SCUB	RCx	pT0pN0	-	Lung	0.4	BSC	DOD 0.6
4	39	M	1	T2N0M0	-	SCUB, UC AC	RCx	pT0pN0	-	Local, L/N, bone, muscle, skin	0.8	EP x 1, IP x 1 irradiation for bone	AWD 1.5
5	53	M	1	T3bN0M0	-	SCUB, UC	RCx	pT3apN0	-	Lung, brain	0.8	Surgical resection for lung, irradiation for brain	DOD 4.3
6	74	M	1	T4aN2M0	Obturator L/N	SCUB, UC	RCx	pT4pN2	-	Muscle, skin	0.3	BSC	DOD 0.4
7	53	M	0	T1N0M0	-	SCUB, UC	RCx	pT0pN0	EP x 2	-	-	-	NED 15.4
8	55	M	0	T2N0M0	-	SCUB, UC AC, SCC	RCx	pT0pN0	EP x 2	Liver	1.7	BSC	DOD 1.9
9	61	F	0	T2N0M0	-	SCUB, UC AC	RCx	pT0pN0	EP x 2	Lung	7.5	EP x 4, prophylactic cranial irradiation	AWD 15.6
10	66	F	1	T4bN2M0	Obturator L/N	SCUB	RCx	pT0pN0	EP x 3[a]	-	-	-	NED 15.3
11	85	F	3	T3bN2M1	Iliac, mediastinal L/N, liver	SCUB	-	-	-	L/N, lung, liver	0.1	BSC	DOD 0.3
12	79	M	2	T3bN3M1	Mediastinal L/N, liver	SCUB, UC	-	-	EP x 1[a]	Lung, liver	0.3	BSC	DOD 0.4

AC = adenocarcinoma; AWD = alive with disease; BSC = best supportive care; DOD = died of disease; DOOD = died of other diseases; ECOG PS = Eastern Cooperative Oncology Group performance status; EP = etoposide + cisplatin; F = female; IP = irinotecan + cisplatin; L/N = lymph node; M = male; NED = no evidence of disease; RCx = radical cystectomy; SCC = squamous cell carcinoma; SCUB = small cell carcinoma of the urinary bladder; UC = urothelial carcinoma.

[a]Presurgical setting.

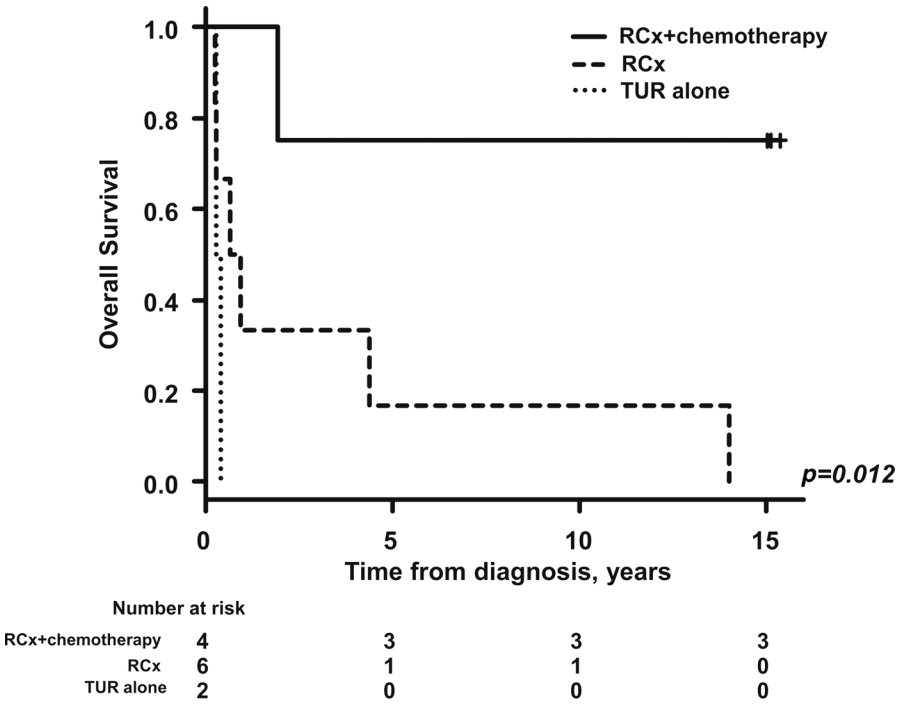

Figure 1. Kaplan-Meier probability curves for overall survival with initial treatment modalities. RCx = radical cystectomy; TUR = transurethral resection.

As a multimodal approach, initial systemic chemotherapy followed by consideration of local therapy, including radical cystectomy, would also be a better management approach for surgically resectable forms of the disease, as it would reduce the risk of pathological upstaging and microscopic metastasis progression.

An analysis using the National Cancer Database revealed the treatment patterns of 625 patients with SCUB. The 3-year OS for neoadjuvant chemotherapy followed by radical cystectomy was 53% compared with 39% for radical cystectomy alone.[5] Siefker-Radtke et al.[13] reported that the outcome of presurgical chemotherapy followed by radical cystectomy was superior to that of initial cystectomy in a series of 46 patients with SCUB at the MD Anderson Cancer Center. In the latest series, 172 cases of SCUB were reviewed. Of the 95 patients with resectable SCUB (≤cT4aN0M0) planned for cystectomy, 48 underwent neoadjuvant chemotherapy and 47 underwent initial cystectomy.[14] Neoadjuvant chemotherapy was associated with a high rate of pathological downstaging and improved survival compared with initial cystectomy (5-year disease-specific survival: 79% vs. 20%, $p < 0.001$). In the subset of patients who received neoadjuvant chemotherapy, those with pathological downstaging had improved survival, whereas those without downstaging did not have favorable outcomes (5-year

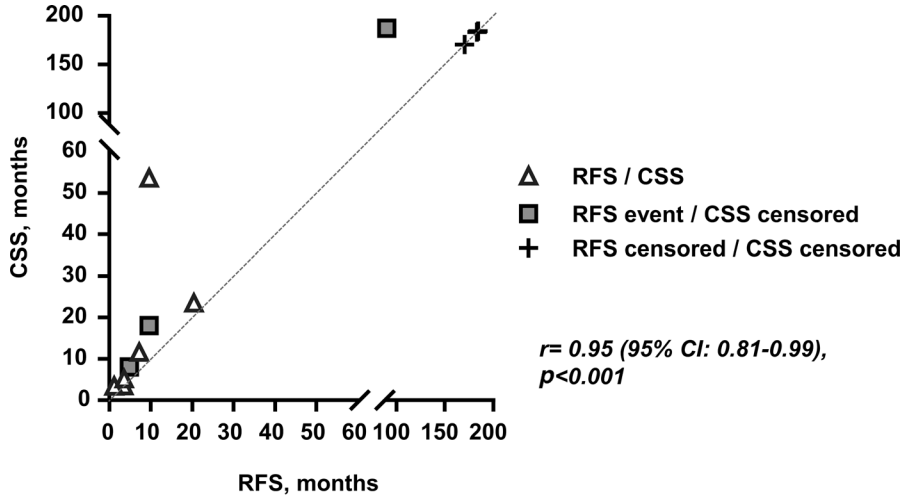

Figure 2. The association between the RFS and the CSS. CI = confidence interval; CSS = cause-specific survival; RFS = recurrence-free survival.

disease-specific survival: 94% vs. 21%, $p < 0.001$). In the future, we must consider whether further chemotherapy should be administered to patients with adverse pathologies despite neoadjuvant chemotherapy.

The optimal regimen and cycle of chemotherapy for SCUB in the perioperative setting remain to be discussed. Although EP or irinotecan and cisplatin with 4–6 cycles is commonly used for small cell lung cancer, the evidence regarding chemotherapy in the perioperative setting is limited to cases after complete resection for stage I disease.[15–17] When small cell lung cancer patients with limited disease are treated with concurrent chemotherapy and radiotherapy, it is recommended that radiation should start early, with 1 or 2 cycles of chemotherapy, so as to not to miss the timing.[18] For SCUB, a retrospective study at the MD Anderson Cancer Center reported a median of 4 cycles of neoadjuvant or adjuvant chemotherapy with mainly EP-based multiagent regimens followed by radical cystectomy.[14] This study showed a more favorable survival rate with neoadjuvant chemotherapy than with adjuvant chemotherapy. We demonstrated that 3 patients who received 3 cycles of neoadjuvant EP or 4 cycles of adjuvant EP had longer survival. Although we cannot conclude which type of chemotherapy, neoadjuvant or adjuvant, provides a better survival benefit, it is important to understand that unfavorable management can lead to the risk of disease progression.

Whether prophylactic cranial irradiation for SCUB improves survival remains unknown. Given the evidence that prophylactic cranial irradiation for small cell lung cancer can be adapted to SCUB, this should be discussed in patients who respond well to chemotherapy.[19,20] Prophylactic cranial irradiation has been shown to be less effective than limited disease for extended disease.[19–21] For SCUB, brain metastases were reported to develop in half of the patients with stage III or higher disease.[22] We encountered 2 patients (no. 2 and 5) who had passed the opportunity for prophylactic cranial irradiation. They had pT3 disease in radical cystectomy alone, and they demonstrated lung and brain metastases coincidentally during follow-up. In contrast, 1 patient (no. 9) with pulmonary metastases after radical cystectomy and adjuvant chemotherapy had long-term survival after chemotherapy and prophylactic cranial irradiation. Thus, the association between disease stage and brain metastasis highlights a subset of patients who may benefit from prophylactic cranial irradiation. In addition, prophylactic cranial irradiation could be useful after systemic chemotherapy when pulmonary metastases develop alone during follow-up.

The present study had some limitations, including its retrospective nature and small sample size. This might have substantially affected the results, especially the outcomes in multiple subgroup settings. However, we demonstrated that radical cystectomy and chemotherapy can be beneficial for patients with resectable disease. For patients with stage T3–4 or N+ disease, initial systemic chemotherapy in the presurgical setting may be an important strategy with which to control disease progression. Further studies are needed to clarify the optimal regimen and the number of cycles of chemotherapy with cystectomy.

5. Conclusions

The outcome of cystectomy alone for resectable SCUB was unfavorable, even in patients with pT0–1. The time from initial progression to death due to cancer was very short, indicating that the initial treatment strategy is crucial. We found that radical cystectomy with chemotherapy (presurgical or adjuvant setting) using an EP regimen improved the prognosis of patients with SCUB with TxNxM0. In addition, prophylactic cranial irradiation may be a treatment option for a subset of patients with advanced disease or pulmonary metastases.

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None.

Statement of ethics

This study has been approved by the institutional review board of Sapporo Medical University (approval number: 342–1003) and the opt-out was applied to their data from all participants. The participants' consent was exempted by the institutional review board due to the retrospective nature of this study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

No conflict of interest has been declared by the author.

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Author contributions

TM: Conceptualization, data curation, investigation, methodology, project administration, formal analysis, and writing;
KH: Investigation, data curation, project administration conceptualization, methodology, writing, supervision;
TS and KS: Investigation, data curation, project administration.
YK, KK, and TT: Investigation, data curation;
NM: Conceptualization, methodology, writing, supervision.

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