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Original Article

Prognostic Values and Treatment Responses Evaluated with Lymphovascular Invasion, Perineural Permeation, and Histologic Transformation for Urothelial Cancer

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Abstract

Background: To evaluate the prognostic significance of adverse pathologic characteristics including lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation in patients with urothelial tumors, and to analyze their correlations with the treatment response to neoadjuvant chemotherapy for bladder cancers. **Materials and Methods:** A total of 277 consecutive patients with muscle-invasive urothelial carcinoma between 2004 and 2016 at China Medical University Hospital in Taiwan were included. Radical cystectomy with extended lymphadenectomy for bladder cancer and radical nephroureterectomy for upper urinary tract cancer were performed. Neoadjuvant chemotherapy was routinely given to patients with bladder cancer. Medical records and adverse pathologic characteristics were reviewed. Overall survival (OS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival were analyzed using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses were carried out using a Cox proportional hazards regression model. The association between pathologic response after neoadjuvant chemotherapy and pathologic characteristics was evaluated using logistic regression. **Results:** Of the 277 patients, 56.3% had at least one adverse pathologic characteristic. Compared to those without adverse characteristics, the patients with at least one adverse pathologic characteristic had significantly worse OS (5-year OS [95% confidence interval (CI)]: 77.2% [65.7%–85.3%] vs. 39.7% [29.9%–49.4%], $P < 0.01$), higher occult nodal metastasis (22.3% vs. 0%), and worse DMFS (5-year DMFS [95% CI]: 88.5% [80.5%–93.4%] vs. 43.0% [33.3%–52.4%], $P < 0.01$). When neoadjuvant chemotherapy was applied, 4.3% of the patients with adverse characteristics achieved a optimal patholoigc response, but 58.1% achieved a pCR, if they did not have any adverse characteristics (odds ratio: 38.8, 95% CI: 6.70–225.2, $P < 0.01$). **Conclusion:** Adverse pathologic characteristics could predict poor outcomes and chemotherapy resistance independently of the clinical AJCC TNM stage in patients with muscle-invasive urothelial carcinoma. Incorporating pathologic information into decision-making for cancer management should be considered.

Keywords: Neoadjuvant therapy, prognosis, urothelial carcinoma

Introduction

Urothelial cancers (UCs) encompass carcinomas of the bladder and upper tract urothelium, including the ureter

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and renal pelvis. Radical nephroureterectomy with bladder cuff excision for upper tract UC (UTUC), and radical cystectomy with lymph node dissection for muscle-invasive bladder cancer (MIBC) constitute the standard treatments for UC.[1-4] Advances in surgical techniques and perioperative care have improved outcomes after radical surgery, however many patients experience relapse, likely from micrometastasis.[5,6] Muscle-invasive carcinoma is associated with a 5-year disease-specific survival rate of 40%–65%. When regional lymph nodes are involved, the 5-year survival rate is 0%–30%.[5,7] Therefore, a major concern for clinicians is the identification of patients at high risk of a poor outcome. New strategies, including the administration of innovative and intensive neoadjuvant therapies, may be able to improve survival in these patients.

Tissue- or blood-based biomarkers that can act as prognostic predictors to improve the outcomes of UC have yet to be incorporated into daily clinical practice.[8] Clinical staging with computed tomography (CT) or nuclear magnetic resonance imaging (MRI) has shown a poor correlation with the pathologic stage.[9,10] Several major pathologic determinants of outcomes in UC patients including tumor stage and surgical margin status after radical surgery are well established;[11] however, in practice it is not possible to apply these pathologic markers in pretreatment planning. Other pathologic characteristics such as lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation can be obtained with a preoperative biopsy; however, their prognostic significance for UC outcomes is still controversial.[12,13]

The purpose of this research was to study the impact of several pathologic characteristics, including lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation on the outcomes of UC patients, and how they correlate with disease relapse and treatment response.

Materials and Methods

Patients and design

We retrospectively reviewed the medical records of all patients with pathologically diagnosed muscle-invasive UC at a tertiary referral center in Taiwan between 2004 and 2016. Patients with concomitant bladder and upper urinary tract tumors, metastatic disease, positive surgical margins after radical surgery, and those who refused or could not tolerate radical surgery were excluded. The clinical stage was based on the pathology report and clinical and radiographic data. Pathologic reports were obtained with transurethral resection of bladder tumors, and ureteroscopy or CT-guided biopsy for upper urinary tract tumors (ureteral and renal pelvic tumors).

For patients with bladder cancer, radical cystectomy with extended lymphadenopathy was performed. Nephroureterectomy with bladder cuff excision was performed for all patients with upper urinary tract tumors; however, routine extended lymphadenectomy was not done unless preoperative CT of the abdomen and pelvis showed lymph node enlargement or palpable lymph nodes during surgery. Regional lymph node recurrence was defined as Kondo's template.[14] Neoadjuvant chemotherapy was routinely administered for patients with bladder cancer before radical cystectomy, but it was not indicated for upper urinary tract tumors. After radical surgery, adjuvant chemotherapy was not routinely recommended; however, it could be administered based on the patient's preference and the physician's discretion. The neoadjuvant chemotherapy regimens consisted of 4 cycles of gemcitabine (gemcitabine 1250 mg/m^2 on day 1, day 8, and day 15 every 4 weeks) and cisplatin (60–75 mg/m^2 on day 1 every 4 weeks). For patients with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, carboplatin was allowed to replace cisplatin.

A chart review was performed to collect the following data: age at surgery, sex, tumor location, chemotherapy status and regimen, renal function (eGFR), tumor pathology (grade, lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation), tumor recurrence, and cause of death.

Tumor stage was determined according to the AJCC TNM classification.[15] Tumor grade was defined according to the 2004 WHO grading system.[16] Lymphovascular invasion was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.[17] Perineural invasion was defined as tumor invasion into the perineural sheath or endoneurium.[18] Renal function was calculated using the abbreviated MDRD equation as GFR = 186 × (serum creatinine/88.4)−1.154 × (age)−×0.203 (0.742 if female).[19] This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of China Medical University and Hospital (IRB approval no. CMUH103-REC1-094; Taichung, Taiwan). The patient's informed consent was waived by the IRB.

Statistical analysis

The following endpoints were assessed: Overall survival (OS), distant metastasis-free survival (DMFS), and locoregional recurrence-free survival (LRFS). Local recurrence was established by urine cytology, cystoscopy and retrograde ureteropyeloscopy and biopsy, and/or CT or MRI scan of the abdomen and pelvis. Distant metastasis was diagnosed based on clinical symptoms, physical examination, and imaging methods. OS was defined as the time from treatment until death; the follow-up of patients still alive was censored at their latest date of follow-up. For analysis of LRFS and DMFS, we recorded the time from the date of treatment to the first locoregional or remote failure, respectively. The presence of a secondary primary transitional cell carcinoma was recorded as locoregional recurrence.

The Chi-squared test or Fisher's test was used to assess between-group differences. All survival data were analyzed using the Kaplan–Meier method with a log-rank test. Univariate and multivariate analyses were carried out using a Cox proportional hazards regression model.

The associations between pathologic response after neoadjuvant chemotherapy and pathologic characteristics were evaluated by calculating odds ratios (ORs) and 95% confidence intervals (95% CIs) with logistic regression. The level of significance was set at $P < 0.05$. Statistical analysis was performed using SPSS statistical software (SPSS Inc., Chicago, IL, USA, version 17.0 for Windows), and EZR,[20] which is a graphical user interface for R (version 2.13.0; The R Foundation for Statistical Computing).

Results

Patient population

A total of 277 patients with UC were identified and included in the study. The median follow-up time after surgery was 25.8 months (mean ± standard deviation: 36.0 ± 1.9 months, range: 0.4–163.2 months). The patients' demographics and pathologic characteristics are listed in Table 1. Overall, 78 patients had bladder cancer, 69 had ureter cancer, and 130 had renal pelvic cancer. The number of females was slightly higher (51.3%). The median eGFR was 46.0 ml/min/1.73 m^2 (mean ± standard deviation: 45.6 ± 27.9 ml/min/1.73 m^2, range 0–150 ml/min/1.73 m^2). Twenty-seven (9.7%) patients had end-stage renal disease requiring hemodialysis. At the end of follow-up, 70 (72.9%) patients had died of cancer-related causes. The estimated 5-year OS, DMFS, and LRFS rates were 56.3%, 63.5%, and 83.8%, respectively.

Most of the patients had high-grade UC (85.2%), 37.2% had lymphovascular invasion, 24.2% had perineural invasion, and 28.2% had squamous or sarcomatoid transformation. In addition, 16 (5.8%), 9 (3.2%), 61 (22.0%), 131 (47.3%), and 60 (21.7%) patients had pathologic stage 0, I, II, III, and IV, respectively.

Univariate analysis [Figure 1] revealed that age >70 years, ECOG >1, advanced clinical stage III-IV, tumors with lymphovascular invasion, perineural permeation, and squamous/sarcomatoid histologic transformation had significant adverse impacts on OS. In particular, the pathologic characteristics of lymphovascular invasion (hazard ratios [HR]: 2.94, 95% CI: 1.96–4.42), perineural permeation (HR: 2.17, 95% CI: 1.43–3.29) and histologic transformation (HR: 2.00, 95% CI: 1.32–3.02) had HR compared to ECOG performance status (HR: 1.93, 95% CI: 1.18–3.15) and clinical stage (HR: 1.58, 95% CI: 1.10–2.74). In contrast, there were no significant differences between sex (male vs. female), eGFR (≤40 vs. >40 ml/min/1.73 m^2), tumor grade (low vs. high), and tumor location (bladder vs. upper urinary tract tumor).

Pathologic adverse factors and clinical outcomes

To evaluate how adverse pathologic characteristics including lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation influenced patient outcomes, we divided the patients into two groups. The patients who had at least one adverse characteristic were classified into the poor prognosis group ($n = 156$), and those who did not have any adverse characteristics were classified into the good prognostic group ($n = 121$).

Table 1: Patient demographics and pathologic characteristics

Characteristics	Overall ($n=277$), n (%)
Age (years), median (range)	70 (26–86)
Sex	
Male	135 (48.7)
Female	142 (51.3)
eGFR, mL/min/1.73 m^2	46 (0–150)
ECOG performance status	
0–1	221 (79.8)
≥1	56 (20.2)
Clinical T stage	
Clinical T1–2	98 (35.4)
Clinical T3–4	179 (64.6)
Clinical N stage	
Node negative	254 (91.7)
Node positive	23 (8.3)
Overall stage	
Stage I–II	95 (34.3)
Stage III–IV	182 (65.7)
Location	
Bladder	78 (28.2)
UTUC	199 (71.8)
Tumor grade	
Low	40 (14.4)
High	236 (85.2)
Pathologic T stage	
T0–T1	25 (9.0)
T2–T4	252 (91.0)
Pathologic N stage	
Node negative	231 (83.4)
Node positive	46 (16.6)
AJCC stage	
Stage 0	16 (5.8)
Stage I	9 (3.2)
Stage II	61 (22.0)
Stage III	131 (47.3)
Stage IV	60 (21.7)
Lymphovascular invasion	
No	174 (62.8)
Yes	103 (37.2)
Perineural invasion	
No	210 (75.8)
Yes	67 (24.2)
Squamous/sarcomatoid transformation	
No	199 (71.8)
Yes	78 (28.2)

eGFR: Estimated glomerular filtration rate, ECOG: Eastern Cooperative Oncology Group, AJCC: The American Joint Committee on Cancer, UTUC: Upper tract urothelial cancer

The survival analysis is shown in Figure 2. The 5-year OS in the good prognostic group was better than that in the poor prognostic group (OS [95% CI]: 77.2% [65.7%–85.3%] vs. 39.7% [29.9%–49.4%], $P < 0.01$). Seventy-five (48.1%) patients in the poor prognostic group died, including 60 (38.4%) due to UC. In comparison, 21 (17.3%) patients

in the good prognostic group died, including 10 (8.3%) due to UC. The 5-year DMFS was markedly different between the good and poor prognostic groups (DMFS [95% CI]: 88.5% [80.5%–93.4%] vs. 43.0% [33.3%–52.4%], $P < 0.01$). However, there was no significant difference in LRFS (LRFS [95%CI]: 88.4% [76.8%–94.4%] vs. 79.5% [69.2%–86.7%], $P = 0.07$) between the two groups.

Multivariate analysis showed that the presence of adverse pathologic characteristics was the most important prognostic factor for OS and DMFS [Table 2]. Clinical stage was also a significantly independent prognostic factor for DMFS.

Since adverse pathologic characteristics were closely associated with distant metastasis, we hypothesized that occult node metastasis would be more common in patients with adverse pathologic characteristics. In our cohort, 254 patients were judged to be free of nodal metastasis according to preoperative imaging studies. Thirty-one of the 139 (22.3%) patients with adverse pathologic characteristics were found to have nodal metastasis in pathologic examinations after surgery, whereas none of the 115 patients without adverse pathologic characteristics had nodal metastasis. Therefore, our results showed that the patients with UC and adverse pathologic characteristics had an intrinsic biological tendency to nodal metastasis and distant dissemination.

Pathologic adverse factors and neoadjuvant chemotherapy

Chemotherapy in the neoadjuvant/adjuvant setting was applied to try and eradicate micrometastasis in the UC patients after radical surgery. Neoadjuvant chemotherapy was routinely administered in the patients with bladder cancer. Corresponding to previous studies,[21,22] a complete or near complete pathologic response (pT0, pT1) after neoadjuvant chemotherapy was associated with better OS.

Of the 78 patients with bladder cancer, 47 (60.3%) had at least one adverse pathologic characteristic, and 31 (39.7%) did not have any adverse factors. After chemotherapy, pathologic evaluations at cystectomy showed that 18 of the 31 (58.1%) patients without adverse factors achieved an optimal pathologic response (pathologic pT0 or pT1), but only 2 of the 47 (4.3%) patients with adverse factors achieved an optimal pathologic response. Multivariate logistic regression analysis revealed that the only statistically significant difference in optimal pathologic response was between the patients with and without adverse pathologic characteristics (OR: 29.34, 95% CI: 5.86–146.85, $P < 0.01$) [Table 3].

Discussion

The results of this study showed that lymphovascular invasion, perineural permeation, and squamous/sarcomatoid transformation could predict occult nodal metastasis, higher incidence of distant metastasis, and poor OS. In addition, the results showed the benefit of contemporary platinum-based neoadjuvant chemotherapy restricted to the patients without these adverse characteristics.

Chemotherapy in the neoadjuvant/adjuvant setting is recommended to decrease the risk of relapse for UC patients. The survival benefit, however, is modest and the toxicities

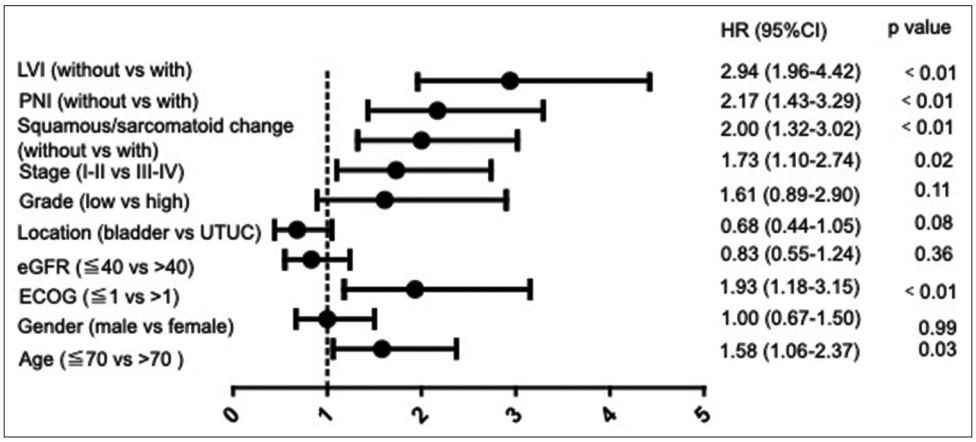

Figure 1: Forest plot showed univariate analysis for overall survival

Table 2: Multivariate analysis of patient outcomes

	OS		DMFS		LRFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Adverse pathologic factors (without vs. with)	3.50 (2.14–5.73)	<0.01	4.80 (2.74–8.42)	<0.01	1.76 (0.86–3.57)	0.12
Age (≦70 vs. >70)	1.51 (0.99–2.29)	0.06	1.39 (0.90–2.16)	0.14	0.54 (0.26–1.12)	0.10
ECOG performance status (0–1 vs. >1)	1.62 (0.97–2.69)	0.07	1.52 (0.88–2.60)	0.13	2.77 (1.21–6.36)	0.02
cStage (I–II vs. III–IV)	1.45 (0.91–2.31)	0.12	1.70 (1.02–2.83)	0.04	1.19 (0.57–2.48)	0.64

HR: Hazard ratio, 95% CI: 95% confidence interval, ECOG: Eastern cooperative oncology group, OS: Overall survival, DMFS: Distant metastasis-free survival, LRFS: Local recurrence-free survival

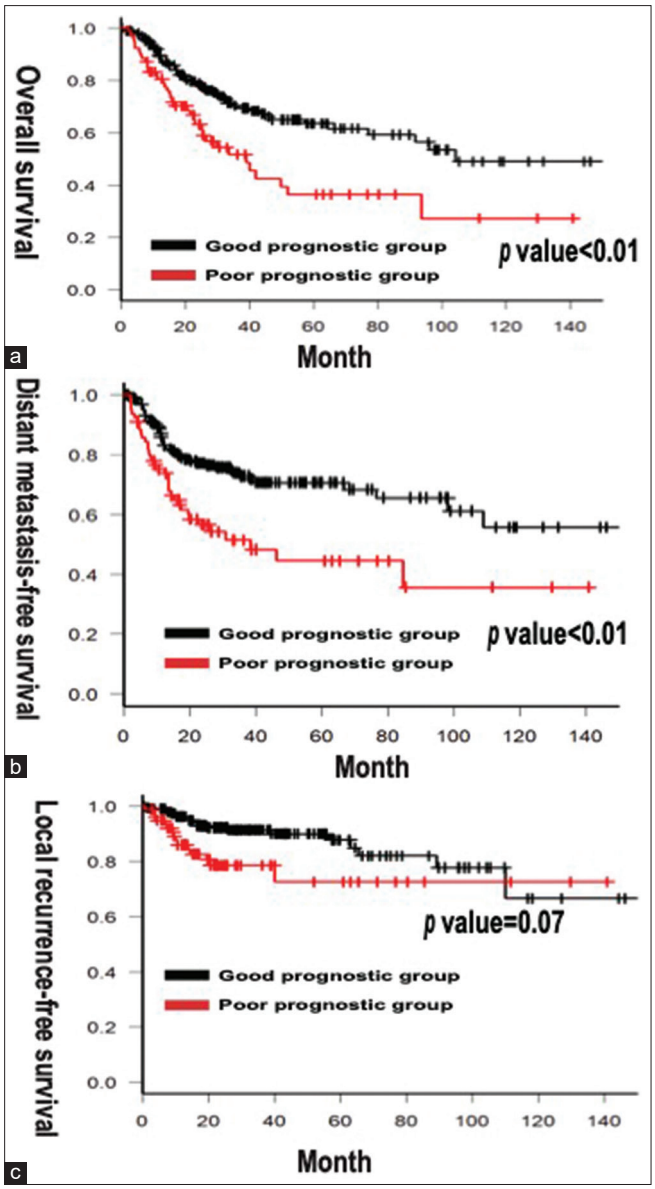

Figure 2: Kaplan–Meier estimation of patient outcomes according to pathologic characteristics. (a) Overall survival analysis; (b) Distant metastasis-free survival; (c) Local recurrence-free survival

are prevalent. For unselected patients with MIBC, only 20% to 30% achieve pT1 or less after neoadjuvant chemotherapy, and reliable risk stratification for identifying respondents is not yet available.[23,24] Baseline clinical stage has been inversely correlated with the likelihood of response to chemotherapy;[11] however, many studies have noted the poor accuracy of clinical staging in UC patients, with the incidence of pathologic upstaging as high as 49% to 72%.[25-27] Lymphovascular invasion is an extensively studied prognostic factor for distant metastasis and poor outcomes, and several studies have suggested that the presence of lymphovascular invasion may predict failure of adjuvant chemotherapy.[28-30] Squamous/sarcomatoid differentiation has been associated with a high recurrence rate after surgery and poorer cancer-specific survival,[31,32] and also poor responses to chemotherapy and radiotherapy.[33,34] Results

Table 3: Multivariate logistic regression analysis of predictors for optimal pathologic response with neoadjuvant chemotherapy

Variables	OR	95% CI	*P*
Adverse pathologic characteristics (without vs. with)	29.34	5.86–146.85	<0.01
Age (≦70 vs. >70)	1.03	0.27–3.90	0.96
ECOG performance status (0–1 vs. >1)	1.35	0.26–6.92	0.72
cStage (I–II vs. III–IV)	2.07	0.42–10.11	0.37

OR: Odds ratio, 95% CI: 95% confidence interval, ECOG: Eastern cooperative oncology group

regarding the prognostic significance of perineural invasion in UC patients treated with radical surgery are contradictory, and little is known about the impact of perineural invasion on the response to chemotherapy.[13,18,35] In our study, nearly 60% of the patients without any adverse pathologic characteristics achieved pT1 or less after neoadjuvant chemotherapy, implying that contemporary neoadjuvant chemotherapy should be applied in this subgroup without being overly concerned about overtreatment. In contrast, fewer than 5% of the patients with at least one adverse pathologic response achieved an optimal pathologic response, suggesting that the combination of cisplatin/gemcitabine is not adequate for optimal cytoreduction of gross tumor before radical surgery and that it should not be recommended under such situations. New strategies involving combinations with novel targeted agents such as angiogenesis inhibitors or immunotherapies should be considered in the setting of clinical trials.

Extended lymphadenectomy is recommended in patients with bladder cancer,[36] but it is still controversial in patients with upper urinary tract cancer. Yoo *et al*. reported that lymph node dissection had no effect on OS and recurrence in patients without suspicious lymph node metastasis on preoperative imaging studies, but that lymphovascular invasion was a risk factor for recurrence and OS.[37] Our study showed that the presence of adverse pathologic characteristics increased the risk of occult nodal metastasis and distant metastasis. Therefore, lymphadenectomy could be selectively performed in patients with clinically node-negative UTUC if a preoperative biopsy reveals adverse pathologic characteristics.

There are several limitations to this study, especially those inherent to retrospective analyses. We excluded patients whose pathologic information from a preoperative biopsy was unavailable for review and those without sufficient clinical information, thus introducing possible selection bias. Second, the patients in this study underwent radical surgery by multiple surgeons, and thus the surgical techniques may have varied. In addition, the pathologic slides were reviewed by multiple pathologists. Nevertheless, it should be noted that surgery was performed by urologic oncologists and pathologists at a tertiary hospital with a high volume of UC. Other pathologic factors such micropapillary and glandular variants were not discussed in this study, which may be associated with

distinguishable clinical outcomes. In our analysis, the patients with an advanced clinical stage still had a trend towards a poorer outcome. This is consistent with clinical expectations, as advanced stages of cancer are generally associated with a higher likelihood of metastasis, treatment resistance, and ultimately lower survival rates. However, the wide CI suggests that while the data showed a trend, the precision of the estimate was low, making it difficult to draw firm conclusions about the true effect size of the clinical stage.

Conclusion

Lymphovascular invasion, perineural permeation and/or squamous/sarcomatoid transformation could predict poor outcomes and chemotherapy resistance independently of clinical AJCC TNM stage in UC patients receiving neoadjuvant chemotherapies. Incorporating pathologic information into decision-making for UC management should be considered.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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