Ongoing Challenges with Clinical Assessment of Nodal Status in T1 Esophageal Adenocarcinoma

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BACKGROUND: Endoscopic mucosal resection (EMR) has emerged as an esophageal-preserving treatment for T1 esophageal adenocarcinoma (EAC); however, only patients with negligible risk of lymph node metastasis (LNM) are eligible. Reliable clinical diagnostic tools for LNM are lacking, as such, several risk assessment scores have been developed. The purpose of this study was to externally validate 2 previously published risk scores (Lee and Weksler) for clinical prediction of LNM in T1 EAC patients.

METHODS: In adherence with the Lee and Weksler scores, esophagectomy patients with pathologic T1 EAC were identified. Sub-analysis was performed in patients with clinical T1 based on EMR. Predictive accuracy of the scores was evaluated by calculating the area under the curve of the receiver operating characteristic curve and calibration plots. The areas under the curves were compared using Venkatraman's test for paired receiver operating characteristic curves.

RESULTS: Of 233 patients identified who met study criteria for external validation, 3 T1a and 32 T1b patients had LNM. The receiver operating characteristic curves demonstrated comparable high predictive and discriminatory capabilities with areas under the curves of 0.832 and 0.824 for the Lee and Weksler scores, respectively ($p = 0.750$). Results were more variable for the EMR cohort. Based on the risk thresholds defined by each score, the false-positive rate compared against the pathologic LNM status were 73% and 56% for Lee and Weksler, with 3% false negatives in the latter. On EMR, the false-positive rates were 70% and 50% for Lee and Weksler, with no false negatives.

CONCLUSIONS: Both scoring systems demonstrated good discriminatory ability and predictive accuracy for LNM, but the defined thresholds resulted in a high false-positive rate. A better scoring system based on clinical characteristics is needed to better identify patients with local disease. (J Am Coll Surg 2019;229:366–373. © 2019 Published by Elsevier Inc. on behalf of the American College of Surgeons.)

Use of endoscopic mucosal resection (EMR) as an organ-preserving therapy for early-stage esophageal cancer has been increasing; however, appropriate patient selection remains challenging. Presence of lymph node metastasis (LNM) is the most important determinant of long-term prognosis in patients with early esophageal adenocarcinoma (EAC).[1,2] It is known that risk of LNM is increased in T1b EAC, with rates of up to 27% reported; however,

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Abbreviations and Acronyms
AUC = area under the curve
EAC = esophageal adenocarcinoma
EGD = esophagogastroduodenoscopy
EMR = endoscopic mucosal resection
EUS = endoscopic ultrasound
LNM = lymph node metastasis

even patients with T1a disease can have a 7% risk.[3,4] As such, EMR should only be offered to patients with low risk of LNM.

Currently available diagnostic tools for evaluation of LNM in early EAC are not acceptably reliable. Fluorine-18 fluorodeoxyglucose PET imaging is limited by frequent tumor non-avidity in early-stage EAC and poor sensitivity in identification of nodal metastasis.[5,6] Endoscopic ultrasound (EUS) has become the gold standard and has been demonstrated to be effective in staging of locoregional disease; however, a recent study by Luu and colleagues[7] demonstrated only 53% T-stage concordance with surgical pathology and 14% unrecognized nodal disease in 139 patients with early disease. Additionally, Barrett's esophagus, often present in EAC, can complicate accurate assessment of nodal status, as a result of increased mucosal nodularity.[8]

Difficulty in identification of patients with LNM has resulted in development of clinical assessment tools using clinicopathologic data to attempt to identify those at high risk. Early studies are limited by small size and inconsistency in patient selection criteria[9-11]; as such, 2 recent studies proposed risk assessment scores specifically for T1 EAC.[12,13] The tools were developed using different data sources, with Lee and colleagues[12] using a single-institutional cohort of 258 patients and Weksler and colleagues[13] using the National Cancer Database. The instruments contain similar input variables (T stage, grade, lymphovascular invasion, and tumor length), but differ to varying degrees in ease of point allocation and score interpretation. Neither instrument has been externally validated to date and, importantly, both studies are limited by their use of pathologic data to create a score meant to be used in the clinical setting.

The objective of this study was to provide external validation of 2 previously published scoring systems for clinical prediction of nodal status in patients with EAC. In addition, we provide additional validation using clinically generated data from patients who underwent diagnostic EMR to determine the clinical utility of these scores.

METHODS

Patients with T1 adenocarcinoma on surgical pathology who underwent esophagectomy without neoadjuvant treatment between 1995 and 2017 were identified from a prospectively maintained institutional database at Memorial Sloan Kettering Cancer Center. In addition, a cohort of patients with T1 disease, as diagnosed by EMR, were identified separately and analyzed to determine the diagnostic performance of these scores using clinical data. Clinicopathologic characteristics were used to validate the scores as defined by Lee and colleagues[12] and Weksler and colleagues[13] (Table 1).

Pathologic characteristics for the validation cohort were identified from final surgical pathology reports. Tumors were staged according to the American Joint Committee on Cancer 7th edition. T1a disease was limited to the mucosa, and T1b invaded the submucosa without involvement of the muscularis propria. Tumor size was defined as the largest measure in any direction. Lymphovascular invasion included identification of tumor cells within surrounding lymphovascular structures. Although grade and tumor length might be determined from esophagogastroduodenoscopy (EGD) with biopsy, the pathology specimens from EGD do not allow for evaluation of lymphovascular invasion and depth of penetration (unlike EMR). As such, we used EGD and EMR to perform a clinical evaluation of the factors included in both scoring systems. T stage, lymphovascular invasion, and grade for the EMR cohort were identified from the EMR specimen report and tumor size was as described in the EGD report.

Characteristics were compared by LNM status using Fisher's exact test and Wilcoxon rank sum test for categorical and continuous variables, respectively. The predictive accuracy of the Lee and Weksler scores was evaluated in the external validation Memorial Sloan Kettering Cancer Center cohort by calculating the area under the curve (AUC). The AUC can be interpreted as the probability that, given 2 randomly drawn patients, the patient with LNM has a higher risk score based on the scoring system. The AUC ranges from 0 to 1, where 0.5 is equivalent to a flip of a coin and 1 represents all patients predicted correctly. The difference between AUCs was assessed using Venkatraman's test for 2 paired curves.[14] The calibration plot is a plot of the predicted risk score probability vs the observed probability of LNM. An ideal scoring system will have all predicted probabilities fall on the 45-degree diagonal line.

Ideally, validation would be performed on the full model coefficients. However, only Lee[12] and colleagues presented the coefficients from the full multivariable model used to construct the nomogram. Therefore, in

Table 1. Comparison and Definitions of the Scoring Systems

Variable	Score A (Lee and colleagues[12])	Score B (Weksler and colleagues[13])
Inclusion criteria	All patients who underwent esophagectomy for EAC with T1 on final pathology	
Location	5 university-affiliated institutions	National Cancer Database
Methodology	Multivariable logistic regression to identify predictive variables for LNM	
Scoring system (variable, points allocated)	Tumor size: cm (+1/cm) Depth: T1a (+0), 1b (+2) Differentiation: Well (+0) Moderate (+3) Poor (+3) LVI: (+6)	Tumor size: mm <15 (+0) 15−25 (+1) >25 (+2) Depth: T1a/b analyzed separately Differentiation: Well (+0) Moderate (+3) Poor (+3) LVI: (+2)
Clinical implication	Risk categories for LNM: Low (0−1 points): <2% Moderate (2−4): 3%−6% High (5+): >7%	Proposed therapeutic algorithm: T1a with score: <4 − EMR + follow-up >4 − Esophagectomy T1b with score: <3 − EMR + follow-up >3 − esophagectomy

EAC, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; LNM, lymph node metastasis; LVI, lymphovascular invasion.

Table 2. Comparison of Demographic Characteristics Between Study Groups

Variable	MSKCC (n = 233)	Lee and colleagues[12] (n = 258)	Weksler and colleagues[13] (n = 1,283)
Years included	1995−2017	2000−2011	2010−2013
Age, y	65 (58−71)*	65.3 (10.1)†	65 (59−71)*
White race, n (%)	217 (93)	NA	1,233 (97.1)
Male sex, n (%)	192 (82)	226 (88)	1,095 (85.3)
Tumor depth, n (%)			
T1a	80 (34)	122 (47)	572 (45)
T1b	153 (66)	136 (53)	711 (55)
Tumor grade, n (%)			
Well differentiated	33 (14)	35 (14)	281 (22)
Moderately differentiated	129 (55)	145 (57)	635 (49)
Poorly differentiated	12 (5.2)	73 (29)	367 (29)
NA	3 (1.3)	—	—
Lymphovascular invasion, n (%)	55 (24)	53 (21)	203 (15.8)
Tumor size, cm	1.7 (0.8−2.5)*	1.7 (1.5)†	1.7 (1.5)†
Nodal metastasis, n (%)			
Overall	35 (15)	44 (17)	146 (11.4)
T1a	3/80 (4)	9/122 (7)	18/572 (3.1)
T1b	32/153 (21)	35/136 (26)	128/711 (18)
Lymph nodes sampled	21 (16−28)*	29.1 (21.5)†	14 (9−21)*
Incomplete resection (any positive margin), n (%)	7 (3)	NA	16 (1.2)
Underlying Barrett's esophagus, n (%)	202 (87)	204 (79)	NA

*Median (interquartile range).
†Mean (SD).
MSKCC, Memorial Sloan Kettering Cancer Center; NA, not applicable.

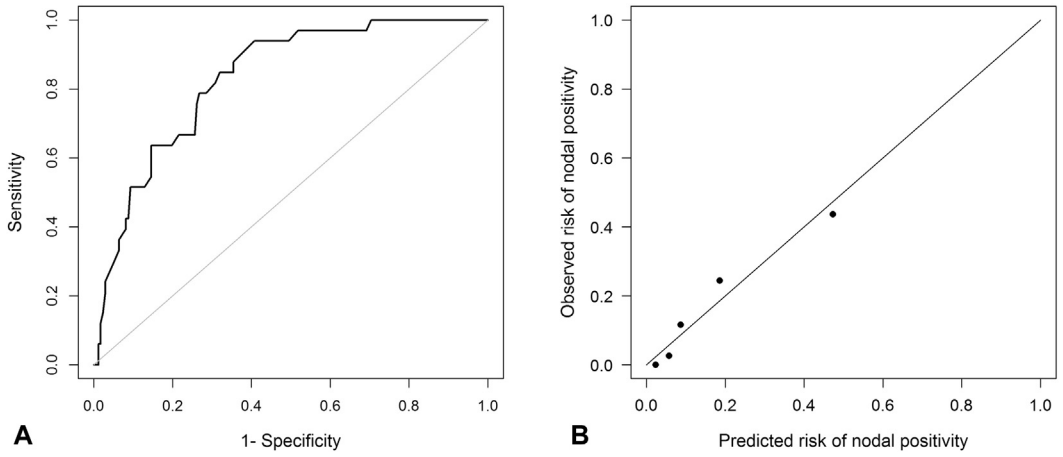

Figure 1. Score A (Lee and colleagues[12]). (A) Receiver operating characteristic curves, (B) calibration plot.

this article, we validated the integer scoring systems provided in each paper. Points were assigned as defined in both papers (Table 1). Validation was also performed on the subset with clinical T1 disease based on EMR report.

Statistical analyses were performed using R, version 3.2.4 (R Foundation for Statistical Computing).

RESULTS

There were 233 patients identified that met study criteria for the external validation; 80 (34%) T1a and 153 (66%) T1b. Lymph node metastasis was identified in 35 (15%) patients. There were 3 (4%) T1a and 32 (21%) T1b patients with LNM. A comparison of the Memorial Sloan Kettering Cancer Center cohort with the other 2 studies is presented in Table 2. Nodal positivity rate ranged from 11% to 15%.

The Lee and Weksler scores had comparable and high discriminatory ability with good predictive accuracy (Figs. 1 and 2) The AUCs were 0.832 (95% CI 0.767 to 0.898) and 0.824 (95% CI 0.755 to 0.892) for the Lee and Weksler scores, respectively. No significant difference in AUC was observed between groups ($p = 0.750$).

There were 58 patients identified that met study criteria for inclusion in the sub-analysis of patients that were identified as T1a on EMR (Table 3). On EMR, 30 patients were diagnosed with T1a disease (52%) and 28 (48%) with T1b disease. Final pathology demonstrated 26 T1a, 28 T1b, and 4 patients with T2 disease. There were 8 (13.8%) patients in this cohort with positive nodal disease. The AUC for the Lee score was 0.919 (95% CI 0.835 to 1.00) compared with the Weksler score, 0.788 (95% CI 0.661 to 0.914). With only 8 events, there were too few bins to plot a calibration curve. Raw plots of predictive value and nodal positivity are shown in Figure 3. The plot for the Lee score (Fig. 3A) demonstrates that node-positive patients are aggregated toward higher predictive values (to the right). For Weksler score

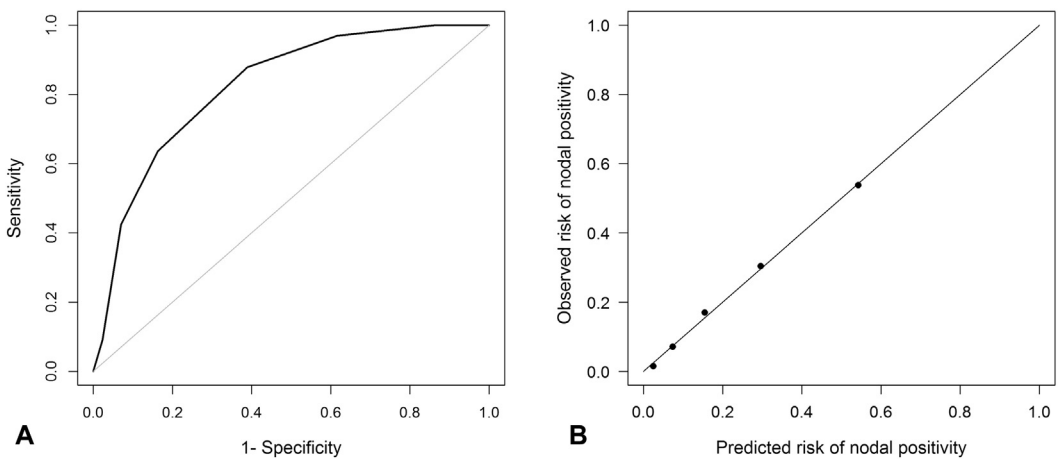

Figure 2. Score B (Weksler and colleagues[13]). (A) Receiver operating characteristic curve, (B) calibration plot.

Table 3. Patient Characteristics in Endoscopic Mucosal Resection Cohort

Characteristic	EMR (n = 58)
Age, y, median (IQR)	63 (56–69)
White race, n (%)	55 (95)
Male sex, n (%)	47 (81)
T stage, EMR, n (%)	
1a	30 (52)
1b	28 (48)
T stage, pathologic, n (%)	
1a	26 (45)
1b	28 (48)
2	4 (7)
Tumor grade, n (%)	
Well differentiated	5 (9)
Moderately differentiated	37 (64)
Poorly differentiated	14 (24)
NA	2 (3)
Lymphovascular invasion, n (%)	21 (36)
Tumor size, cm, median (IQR)	1.5 (1–2)
Nodal metastasis, n (%)	
Overall	8 (14)
Underlying Barrett's esophagus, n (%)	52 (90)

EMR, endoscopic mucosal resection; IQR, interquartile range; NA, not applicable.

(Fig. 3B), predicted risk was underestimated for several node-positive patients (see triangles on far left).

The accuracy of the Lee and Weksler scores was calculated based on the high-risk thresholds defined in the respective papers. Compared with pathologic staging, the false-positive rate in the external validation cohort was 73% (95% CI 66% to 80%) and 56% (95% CI 48% to 63%) for the Lee and Weksler scores, respectively, with a 3% false-negative rate in the latter (Table 4). In the EMR cohort, the false-positive rates were 70% (95% CI 51% to 85%) and 50% (95% CI 31% to 69%) for Lee and Weksler, respectively, with a 0% false-negative rate for both (Table 5).

DISCUSSION

Endoscopic mucosal resection has been used increasingly as organ-preserving treatment for patients with early-stage esophageal adenocarcinoma; however, its use is dependent on accurate diagnosis of LNM. Determination of LNM is limited in accuracy by currently available clinical tools. This study used a large single-institutional cohort to compare 2 LNM scoring systems developed previously for assessment of risk of LNM for T1 EAC. Our external validation cohort was similar to those of the 2 studies under evaluation. Additionally, as demonstrated elsewhere, our cohort had a nodal positivity rate of 4% in T1a patients and 21% in T1b patients. The discriminatory performance of the 2 scores on external validation was high (AUC >0.8), with no significant difference between AUCs and excellent predictive accuracy on calibration plots. To minimize the rate of missed LNM, the thresholds defined as high risk by both scores resulted in a high rate of false positives. The 2 assessed studies are further limited by their use of pathologic data in creation of a scoring system meant for clinical use.

In the current era, it has become increasingly important to identify appropriate candidates for organ-preserving therapy for early-stage esophageal cancer as the implications of undertreatment are grave. In a theoretically low-risk cohort of node-negative EAC patients treated with esophagectomy, we recently demonstrated 5-year

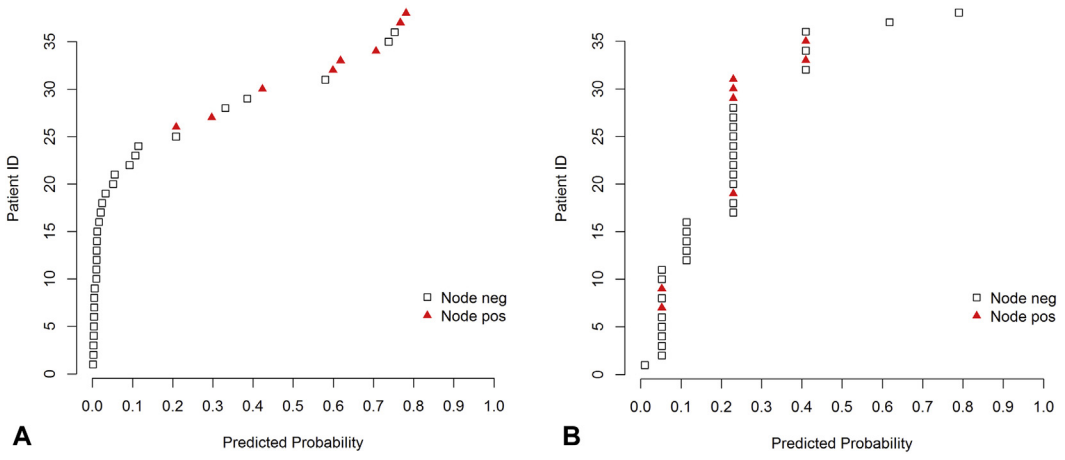

Figure 3. Plot of predicted values and nodal positivity in endoscopic mucosal resection subset. (A) Score A, (B) score B.

Table 4. Measures of Accuracy for Lee and Weksler Scores in the Pathologic Cohort

Score	Negative LN, n (n = 172)	Positive LN, n (n = 33)	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Lee						
Low	46	0	100	26.7	20.8	100
High	126	33	100	26.7	20.8	100
Weksler						
Low	76	1	97	44.2	25	98.7
High	96	32	97	44.2	25	98.7

LN, lymph node.

recurrence rates of 8.2%, 11.5%, and 22.2% for pathologic T1a, T1b, and T2, respectively.[15] Lymphovascular invasion, which is closely associated with T stage, was an important predictor of recurrence, and recurrence was associated with poor prognosis. These findings highlight the importance of careful patient selection for EMR given that even among the lowest-risk patients, there is a significant risk of recurrence.

Unfortunately, current clinical staging is limited by the ability of available diagnostic tools to accurately identify T stage and LNM. Although EUS has been demonstrated to have accuracy of up to 97% in identification of tumor depth, the role of this modality remains controversial in evaluation of early disease, with variable outcomes ranging from 53% to 99%.[7,16,17] Although EUS has variable performance in assessing pathologic T stage, limited data have suggested the utility of EMR as a staging tool. Pouw and colleagues[18] found that in 105 patients with unremarkable EUS findings, EMR identified submucosal invasion in 17 (24%). In our series, EMR demonstrated 72% (42 of 58) of T-stage concordance with surgical pathology compared with 35% (17 of 49) with EUS. These findings highlight the importance of EMR as a diagnostic tool for more accurate T staging. Similarly, assessment of LNM on imaging and EUS is also flawed.[6-8] Although the addition of fine-needle aspiration to EUS is associated with reasonable reliability (sensitivity 75% and specificity 95%), identification of high-risk nodes is difficult.[19] As demonstrated in a series of 25 patients evaluated with EUS, the ability of echo features (size, hypoechoic, margins, and shape) to distinguish between benign and malignant nodes was 80% when all 4 features were present; however, only 25% of malignant nodes had all 4 features.[20] In addition, EUS with fine-needle aspiration is complex to perform because it often requires traversing the tumor with the needle, and risks seeding. By using pathologic staging to identify T1 node-negative patients, the authors of the 2 studies fail to account for this known discordance in clinical staging. As such, we performed a sub-analysis using clinically obtained data to determine the performance of the 2 scores in the preoperative setting, as they would theoretically be used in routine clinical practice to guide treatment selection.

Our sub-analysis using patients with EMR suggested more variation between the scoring systems, with the Lee score appearing to have higher discriminatory ability for risk of LNM (AUC 0.919 compared with 0.788 for the Weksler score). The significance of the observed difference between scores was likely limited by our small sample size. In addition, the clinical utility of these scores remains unknown based on this analysis as neither score accounted for the known discordance between clinical and pathologic T staging in its development. It seems appropriate that a score meant for clinical use must use measures taken from clinical data.

Although understaging and undertreatment can have devastating prognostic consequences, overstaging is also problematic in that it limits the use of local therapy in place of esophagectomy. Therefore, another important consideration in predicting LNM is the tradeoff between

Table 5. Measures of Accuracy for Lee and Weksler Scores in the Endoscopic Mucosal Resection Cohort

Score	Negative LN, n (n = 30)	Positive LN, n (n = 8)	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Lee						
Low	9	0	100	30	28	100
High	21	8	100	30	28	100
Weksler						
Low	15	0	100	50	35	100
High	15	8	100	50	35	100

LN, lymph node.

false positives, resulting in unnecessary esophagectomy, and false negatives, resulting in missed LNM. The cutoffs specified by both scores resulted in a high false-positive rate (>50%) in both the validation and EMR cohorts. The lower false-positive rate in the validation cohort for the Weksler score was offset by the false-negative rate of 3%. In contrast, although the Lee score had a 73% false-positive rate, there were no false negatives. Future scoring systems might include additional factors that allow for minimization of false positives without compromising the ability to capture all patients with LNM.

Our study confirmed the predictive ability of 2 proposed risk assessment scores for LNM in T1 EAC and evaluated their utility in the clinical setting. There are several limitations to this study. Our external validation demonstrated no significant differences between the discriminatory abilities and similar predictive accuracy between the 2 studies. Based on AUC, both models performed well. However, the choices of cutoff specified might favor sensitivity (100% for Lee and 97% for Weksler) over specificity (27% and 44%, respectively). Second, we included a long study period to identify a sufficient sample size. However, given that the input variables used for both scoring systems are obtained from pathologic specimens rather than imaging modalities, it is unlikely that developments in diagnostic technology are likely to have impacted the results of the external validation portion of this study. Finally, the results of the EMR cohort must be interpreted with caution given the small sample size and highly selected patients. Patients that undergo esophagectomy after EMR include those with either positive margins after EMR or higher-risk features.

CONCLUSIONS

This study demonstrated that both scoring systems (Lee and Weksler)[12,13] had good predictive accuracy on external validation and performed well in a sub-analysis using clinical data. Although the identified variables used in the 2 scoring systems are clearly important to determination of LNM, additional study is needed to identify whether these and other clinical variables are of use in the clinical setting to better predict LNM and also allow for fewer patients to undergo unnecessary esophagectomy. Given the differences in LNM between patients with T1a and T1b disease, we do recommend that patients with early esophageal cancer undergo diagnostic EMR to better assist in clinical decision-making and risk assessment.

Author Contributions

Study conception and design: Sihag, Jones, Molena, Bains, Hsu, Tan

Acquisition of data: Nobel, Barbetta

Analysis and interpretation of data: Hsu, Tan, Nobel, Molena, Barbetta

Drafting of manuscript: Hsu, Tan, Nobel, Molena

Critical revision: Sihag, Bains, Jones, Molena, Hsu, Tan

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