

Regression Derived Staging Model to Predict Overall and Disease Specific Survival in Patients With Major Salivary Gland Carcinomas With Independent External Validation

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PURPOSE The current American Joint Cancer Committee (AJCC) staging system for salivary gland tumors does not include histology and grade in its classification despite their proven prognostic importance. We planned to analyze if a modified staging system integrating these two factors into the staging improves prognostic performance and then validate it externally.

MATERIALS AND METHODS From SEER database (2000-2018), patients with major salivary gland carcinoma who underwent surgical resection between 2004 and 2015 were analyzed. Histologies were recoded into two groups based on grade and type of histology into “Low Aggression” and “High aggression” groups. Cox proportional hazards model was used to identify predictor variables for overall survival and disease-specific survival and models were generated based on least absolute shrinkage and selection operator regression. Model performance was evaluated by Akaike Information Criterion, concordance index and calibration plot. The best model chosen was externally validated from our hospital database of patients who underwent surgery for salivary gland tumor between January 1, 2012 to December 31, 2019.

RESULTS Six thousand two hundred forty-six patients were analyzed with a median follow up of 58 months. Age > 65 years, male sex, metastatic disease, Histological Stratification, Grade of tumor, AJCC stage and Primary Site were the significant factors influencing overall survival and disease-specific survival. By least absolute shrinkage and selection operator regression method, Correlation analysis and Interaction testing by multiple regression, AJCC stage and Histological Risk stratification were used for generating four models, out of which the best model was selected by Akaike Information Criterion, C index and calibration plot. This model was then externally validated in our hospital database of 269 patients.

CONCLUSION We propose an externally validated modified salivary gland staging system that incorporates histology and grade of tumor for improved hazard discrimination among patient subgroups.

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INTRODUCTION

Major salivary gland tumors are a rare group of tumors with varied guidelines on its treatment. The main reason for this is that there are a variety of prognostic factors like tumor grade and histology in addition to those proposed in the current American Joint Cancer Committee (AJCC) staging system (8th edition). Though these were identified as prognostic factors, no study has been conducted incorporating both into the current AJCC staging to improve hazard discrimination and hazard consistency across different stages. In the present study, we used data of salivary gland tumors from the SEER database to develop a predictive model incorporating tumor grade and histology into the AJCC system and validated it externally.

Aims and Objectives

Primary objectives.

1. To assess if tumor grade and degree of aggression as determined by WHO 2017 histological classification system of salivary gland tumors influences overall survival (OS) and disease-specific survival (DSS).
2. To generate a new modified staging system incorporating the above into the existing staging system (AJCC 8th edition)

Secondary objectives.

1. External validation of the modified staging system in our hospital database based in India.

MATERIALS AND METHODS

This study is an analysis on cases collected in US National Cancer Institute’s SEER database (November

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

As tumor grade and histology are important prognostic factors for overall and disease-specific survival, should they be included in the current TNM staging system of major salivary gland carcinomas?

Knowledge Generated

Incorporation of tumor histology and grade as a combination resulted in better hazard discrimination of patients with major salivary gland carcinomas sampled from a large population database. Models were generated based on the above findings and one was chosen based on statistical indices. Our result was then externally validated from our hospital database independently, yielding similar results.

Relevance

The proposed staging system will result in better prognostication of patients with major salivary gland carcinomas and can be easily implemented in clinical practice as we have externally validated the model.

2020 submission). The “Incidence – SEER Research Data, 18 registries, Nov 2020 sub (2000-2018)” database was used in collection of cases diagnosed with salivary gland malignancies between 2004 and 2015. Using the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) classification the following histological codes were used for case listing from the database: 8000/3,

8001-8005//3, 8010-8015/3, 8020-8022/3, 8030-8035/3, 8050/3, 8052/3, 8200/3, 8201/3, 8202/3, 8140/3, 8143/3, 8147/3, 8070-76/3, 8082-8084/3 and 8078/3. The subsite of the salivary gland site was classified using the following primary site ICD-O-3 codes: C07.9-Parotid gland, C08.0-Submandibular gland, C08.8-Overlapping lesion of major salivary glands and C08.9-Major salivary gland, not

FIG 1. Study flowchart. (A) Development cohort. (B) Validation cohort.

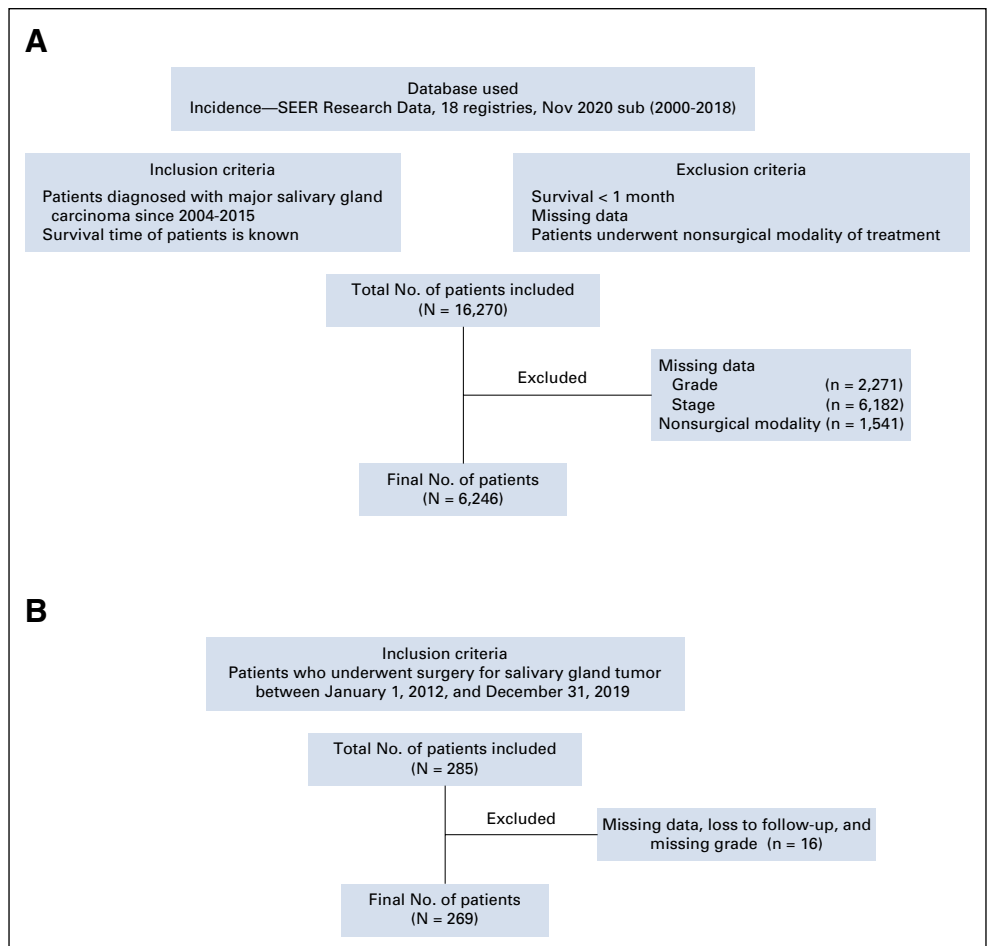


TABLE 1. Demographic Details

Variable	SEER Database Cohort (N = 6,246)	External Validation Cohort (N = 269)
Age, years, No. (%)		
< 65	3,059 (49)	227 (84.4)
More than 65	3,187 (51)	42 (15.6)
Sex, No. (%)		
Male	3,761 (60.2)	156 (58)
Female	2,485 (39.8)	113 (42)
Primary site, No. (%)		
Parotid gland	5,245 (84)	243 (90.3)
Submandibular gland	812 (13)	25 (9.3)
Major gland NOS	189 (3)	1 (0.4)
Grade of tumor, No. (%)		
Low grade	1,101 (17.6)	99 (36.8)
Intermediate grade	2,297 (36.8)	62 (23)
High grade	2,848 (45.6)	108 (40.1)
WHO histological aggression, No. (%)		
Low aggression	2063 (33)	151 (56.1)
High aggression	4,183 (67)	118 (43.9)
AJCC stage, No. (%)		
I	1758 (28.1)	78 (29)
II	1,117 (17.9)	83 (30.9)
III	1,336 (21.4)	48 (17.8)
IVA	1,652 (26.4)	51 (19)
IVB	207 (3.3)	2 (0.7)
IVC	176 (2.8)	7 (2.6)
Histology, No. (%)		
MEC	2,343 (37.5)	108 (40.8)
Adenoidcystic carcinoma	475 (7.6)	37 (14)
SDC	217 (3.5)	30 (11.3)
MASC	26 (0.4)	10 (3.8)
EMC	136 (2.2)	26 (9.8)
Adenocarcinoma	926 (14.8)	11 (4.2)
SCC	35 (0.6)	9 (20.5)
Acinic cell carcinoma	Nil	18 (6.8)
Lymphoepithelial carcinoma	45 (0.7)	3 (1.1)
Carcinoma NOS	2043 (32.7)	13 (4.9)
Neck dissection, No. (%)		
Sampling only	1,409 (22.6)	137 (50.9)
Neck dissection done	3,171 (50.8)	113 (42)
Not done	1,666 (26.7)	19 (7.1)

Abbreviations: AJCC, American Joint Cancer Committee; EMC, epithelial myoepithelial carcinoma; MASC, mammary analogue secreting carcinoma; MEC, mucoepidermoid carcinoma; NOS, not otherwise specified; SCC, squamous cell carcinoma; SDC, salivary duct carcinoma.

TABLE 2. Candidate Staging Models for Primary Tumor Staging of Salivary Gland Tumors

Staging System	Description
Model 1	
Stage I	WHO low aggression
Stage II	WHO high aggression
Model 2	
Stage I	AJCC 8th stage I + WHO low aggression
Stage II	AJCC 8th stage II/III + WHO low aggression
Stage III	AJCC 8th stage I/II + WHO high aggression AJCC 8th stage IVA/IVB/IVC + WHO low aggression
Stage IVA	AJCC 8th stage III + WHO high aggression
Stage IVB	AJCC 8th stage IVA/IVB + WHO high aggression
Stage IVC	AJCC 8th stage IVC + WHO high aggression
Model 3	
Stage I	AJCC 8th stage I/II/III + WHO low aggression
Stage II	AJCC 8th stage I + WHO high aggression AJCC 8th stage IVA/IVB + WHO low aggression
Stage III	AJCC 8th stage II + WHO high aggression
Stage IVA	AJCC 8th stage III + WHO high aggression
Stage IVB	AJCC 8th stage IVA/IVB + WHO high aggression
Stage IVC	AJCC 8th stage IVC + WHO low/High aggression
Model 4	
Stage I	AJCC 8th stage I/II/III + WHO low aggression
Stage II	AJCC 8th stage I + WHO high aggression AJCC 8th stage IVA/IVB + WHO low aggression
Stage III	AJCC 8th stage II + WHO high aggression AJCC 8th stage IVC + WHO low aggression
Stage IV	AJCC 8th stage III + WHO high aggression AJCC 8th stage IVA/IVB/IVC + WHO high aggression

Abbreviation: AJCC, American Joint Cancer Committee.

otherwise specified. Using these inclusion criteria, the total number of cases included were 16,270. Cases with missing data (Grade, T, N and M stage), not undergoing surgery (n = 541) were removed from analysis resulting in the final cohort of 6,246 patients (Fig 1A). The variables corrected were age, sex, race, primary site, grade, histology as per ICD-O 3 system, T stage, N stage, M stage and stage grouping as per TNM 8th edition, surgery details, lymph node dissection details, survival in months and status at close of database entry (November 2020). Primary sites were recoded as Parotid gland, Submandibular gland and Major Salivary glands NOS. Histologies were recoded into two groups as per Histological Risk stratification used in WHO 2017 classification based on grade and type of histology into “Low Aggression” and “High aggression” groups.¹

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 20 (IBM Corp, Armonk, NY). The clinical

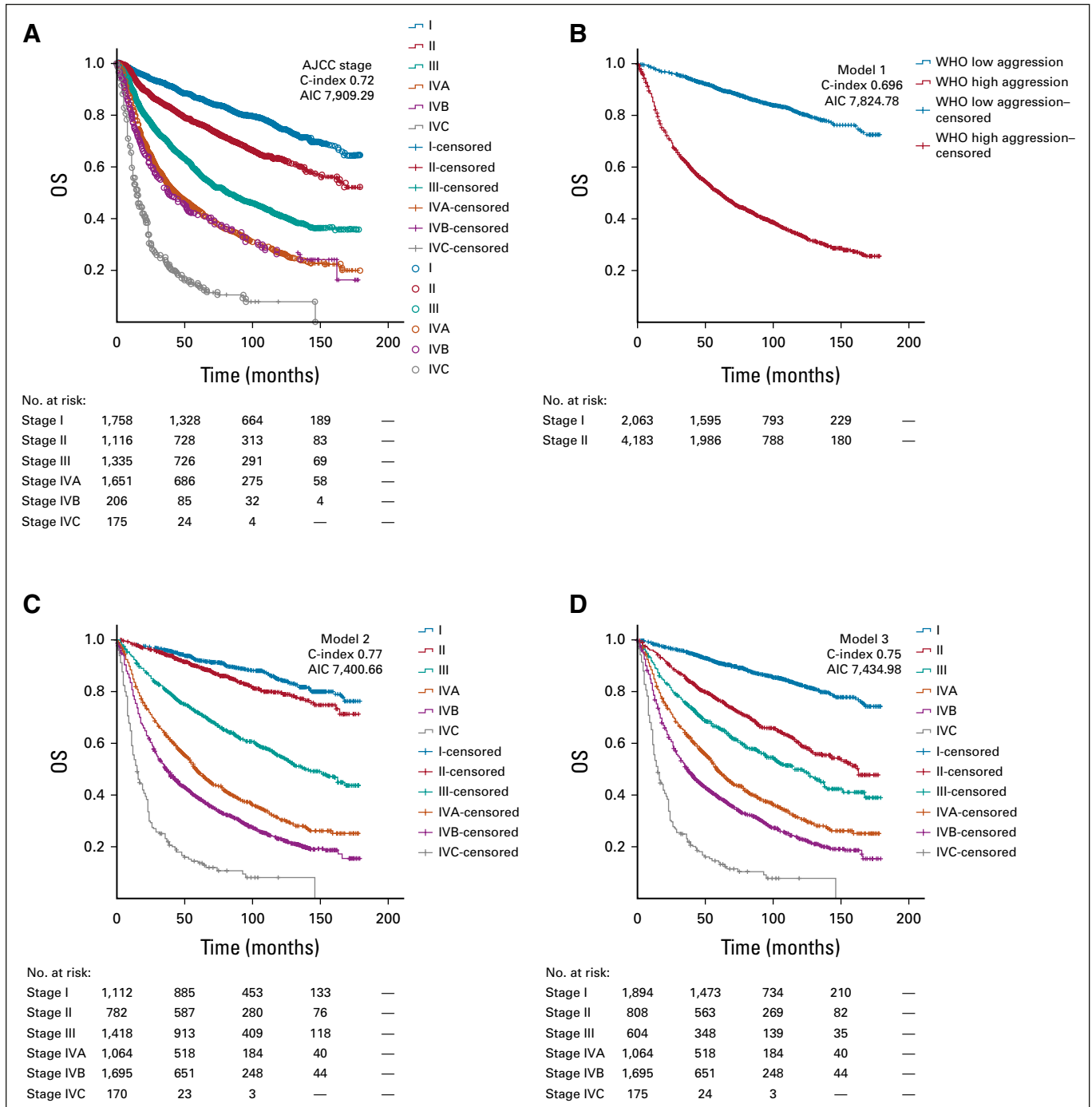


FIG 2. Kaplan-Meier plots (OS With 95% CIs) in development cohort (A) based on Current AJCC (8th ed) staging system, (B) based on Model 1 staging system, (C) based on Model 2 staging system, (D) based on Model 3 staging system, and (E) based on Model 4 staging system. AIC, Akaike Information Criterion; AJCC, American Joint Cancer Committee; C-index, concordance index; OS, overall survival.

end points were OS and DSS. We first sought to determine if grade of tumor and histology of the tumor provides significant prognostic information beyond T, N and M categories in multivariable-adjusted models. Cox regression analysis was done to look at covariates influencing OS and DSS. To select predictor variables, the least absolute

shrinkage and selection operator regression was adopted. After correlation analysis and interaction testing by multiple regression, predictors were selected for model generation after removing predictors with significant interaction and multicollinearity. On the basis of this, four candidate primary tumor staging systems were generated. All four

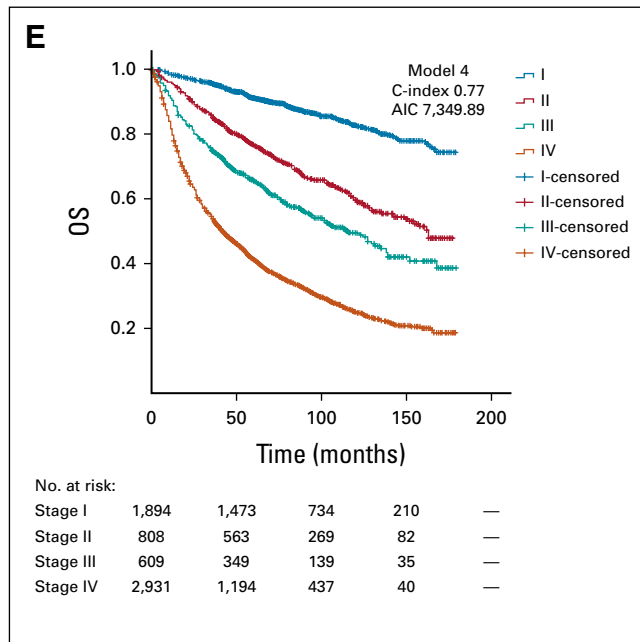


FIG 2. (Continued).

models were tested for discriminative performance by Akaike Information Criterion (AIC), Calibration plot, the Harrel concordance index (C-index), and Visual inspection.

Because predictive models perform better in the data from which they were derived than on external data, an independent external validation of these models was done from the database from our hospital. Approval from institutional review board was obtained before undertaking this analysis. Patients who underwent surgery for salivary gland tumor between January 1, 2012 and December 31, 2019 were taken for analysis. The variables collected were age, sex, race, primary site, grade, histology as per ICD-O 3 system, T stage, N stage, M stage and stage grouping as per TNM 8th edition, surgery details, lymph node dissection details, survival in months and status at close of database entry (February 26, 2022). A total of 285 patients met the inclusion criteria. Missing data, loss of follow up resulted in exclusion of 16 patients leaving 269 patients for final analysis (Fig 1B). The models generated from the SEER database were applied to this database and their performance was assessed by the Harrel C-index, Calibration plots, AIC and visual inspection. This study was conducted and reported in accordance with Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis system (Checklist and assessment form in Data Supplement).² All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

A total of 6,246 patients were included for analysis with median follow up of 58 months. The demographic data are

presented in Table 1. The median age of the study cohort was 65 with standard deviation (SD) of 17.6 years. Around 40% were females and 60% were males. Eighty-four percentage of patients had Parotid gland as the primary site while 13% had submandibular gland tumors. The distribution of tumor grades was as follows: Low grade constituted 17.6%, Intermediate 36.8% and High grade totaled 45.6% of the cohort. Mucoepidermoid carcinoma was the most common histology (37.5%) followed by Squamous carcinoma at 19.7% and Adenocarcinoma at 10.6%. All patients had undergone major salivary gland resection while 50.8% had undergone neck dissection, 21.6% had undergone lymph node sampling and 24.5% did not undergo neck dissection or sampling. A total of 28.2% were Stage I (AJCC 8th edition) tumors, 17.9% were Stage II, 21.4% were Stage III, 26.4% were Stage IVA and 3.3% had Stage IVB tumors. 2.8% had distant metastasis at presentation. 67.6% had NO stage. Based on WHO 2017 pathological classification, the cohort was divided into low aggression (33%) and high aggression (67%) based on tumor histology and grade of tumor.

At 10 years, the baseline hazard for OS and DSS of this cohort was 0.711 (SD 0.008) and 0.408 (SD 0.008) respectively. Analysis by Cox proportional hazard model showed that age > 65 years (hazard ratio [HR], 2.72; 95% CI, 2.49 to 2.97), male sex (HR, 1.24; 95% CI, 1.14 to 1.35), metastatic (M1) disease (HR, 3.8; 95% CI, 2.86 to 5.05), WHO stratification high risk (HR, 2.38; 95% CI, 2.06 to 2.74), grade of tumor (Intermediate and High—HR, 1.2; 95% CI, 1.02 to 1.41), AJCC stage (HR, 1.81; 95% CI, 1.11 to 2.96) and primary site (Parotid gland HR, 1.18; 95% CI, 1.05 to 1.32) were the significant factors influencing OS. Age > 65 years (HR, 2.17; 95% CI, 1.95 to 2.42), male sex (HR, 1.2; 95% CI, 1.12 to 1.41), M1 disease (HR, 11.53; 95% CI, 8.905 to 14.94), WHO Risk stratification High Risk (HR, 5.023; 95% CI, 3.828 to 6.592), Grade (Intermediate and High—HR, 2.051; 95% CI, 1.51 to 2.76), AJCC Stage (HR, 5.64; 95% CI, 4.313 to 7.398) and Primary Site (Parotid Gland HR, 1.23; 95% CI, 1.070 to 1.418) were the significant predictors for DSS. Least absolute shrinkage and selection operator regression method was used to select variables for the model by which Primary site was removed. Correlation analysis and interaction testing was done by multiple regression This showed that WHO stratification and stage had the highest correlation with both OS and DSS while Age, grade sex and M1 status had intermediate correlation and also showed multicollinearity (between age and sex; M1 status and stage; grade and histological risk stratification). Removal of covariates with intermediate correlation and multicollinearity did not affect model performance. Addition of histological risk stratification to AJCC stage resulted in a better fit as evidenced by reduced AIC index. Hence these two covariates were used for generating four candidate staging systems (Table 2).

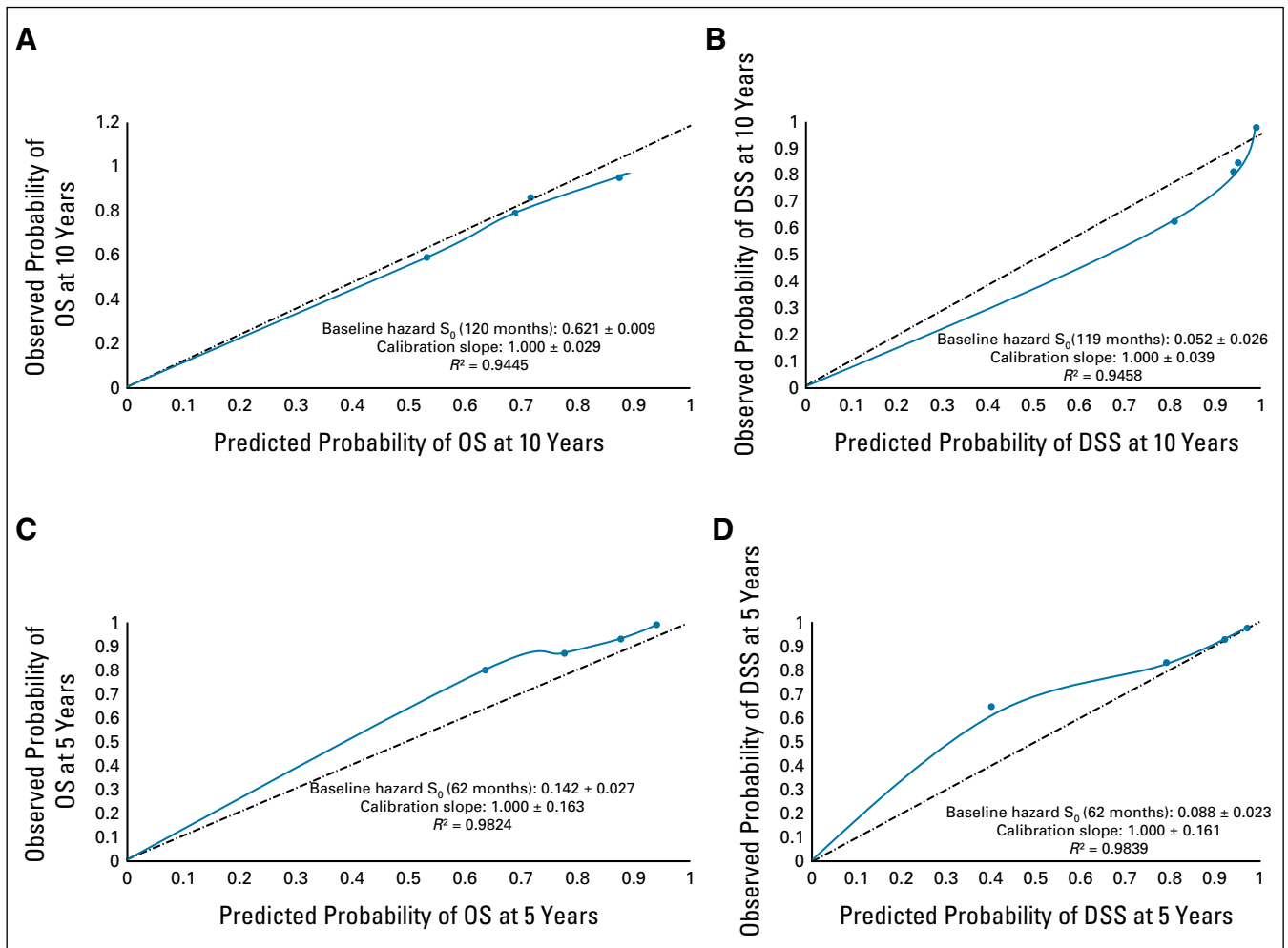


FIG 3. Calibration plots. (A,B) Calibration plot for development cohort. (C, D) Calibration Plot for validation cohort. DSS, disease-specific survival; OS, overall survival.

Model 1 used only Histological risk stratification and had two stages. This model performed poorly as compared to others and AJCC system (Fig 2). This showed that AJCC staging system cannot be replaced and that these two factors act in a complementary fashion in predicting survival. As shown in Figure 2, the current AJCC staging system performed poorly in regard to discrimination and stratification of IVA and IVB disease with considerable overlap in 95% CIs. Model 2 and 3 performed poorly in discriminating IVA and IVB in addition to poor discrimination of Model 2 between stage I and II due to overlapping 95% CIs. Models 4 had good discrimination between the stages with no overlapping 95% CIs, lower C index and higher AIC as compared to others (Fig 2). Of the candidate staging systems, Model 4 was preferred based on relative simplicity, lower AIC (7,349.89), higher C-index (0.77 with sSE of 0.006), better calibration (baseline hazard of 0.621 [SD 0.009] and R^2 value of 0.9445), better Stratification of patients into distinct prognostic groups with well separated curves on visual inspection and minimal overlap of 95% CIs (Figs 2 and 3). Similar results were

obtained for DSS. Model 4 performed the best in stratification of patients (Figs 3 and 4).

External validation was done from our hospital data of 269 patients with median follow up of 55 months. Demographic details are depicted in Table 1. The median age of the validation cohort was 48 (SD 15.9 years) with 58% of them being males. Parotid gland was the most common subsite (90.3%). The distribution of tumor grades was as follows: Low grade constituted 36.8%, Intermediate 23.1% and High grade totaled 40.1% of the cohort. Mucoepidermoid carcinoma was the most common histology (40.5%) followed by Adenoidcystic carcinoma at 13.7%. All patients had undergone major salivary gland resection while 41.6% had undergone neck dissection, 50.9% had undergone lymph node sampling and 7.5% did not undergo neck dissection or sampling. 29% were Stage I (AJCC 8th edition) tumors, 30.9% were Stage II, 17.8% were Stage III, 19% were Stage IVA and 0.7% had Stage IVB tumors. 2.6% had distant metastasis at presentation. 83.6% had NO stage. Based on WHO 2017 pathological classification, the

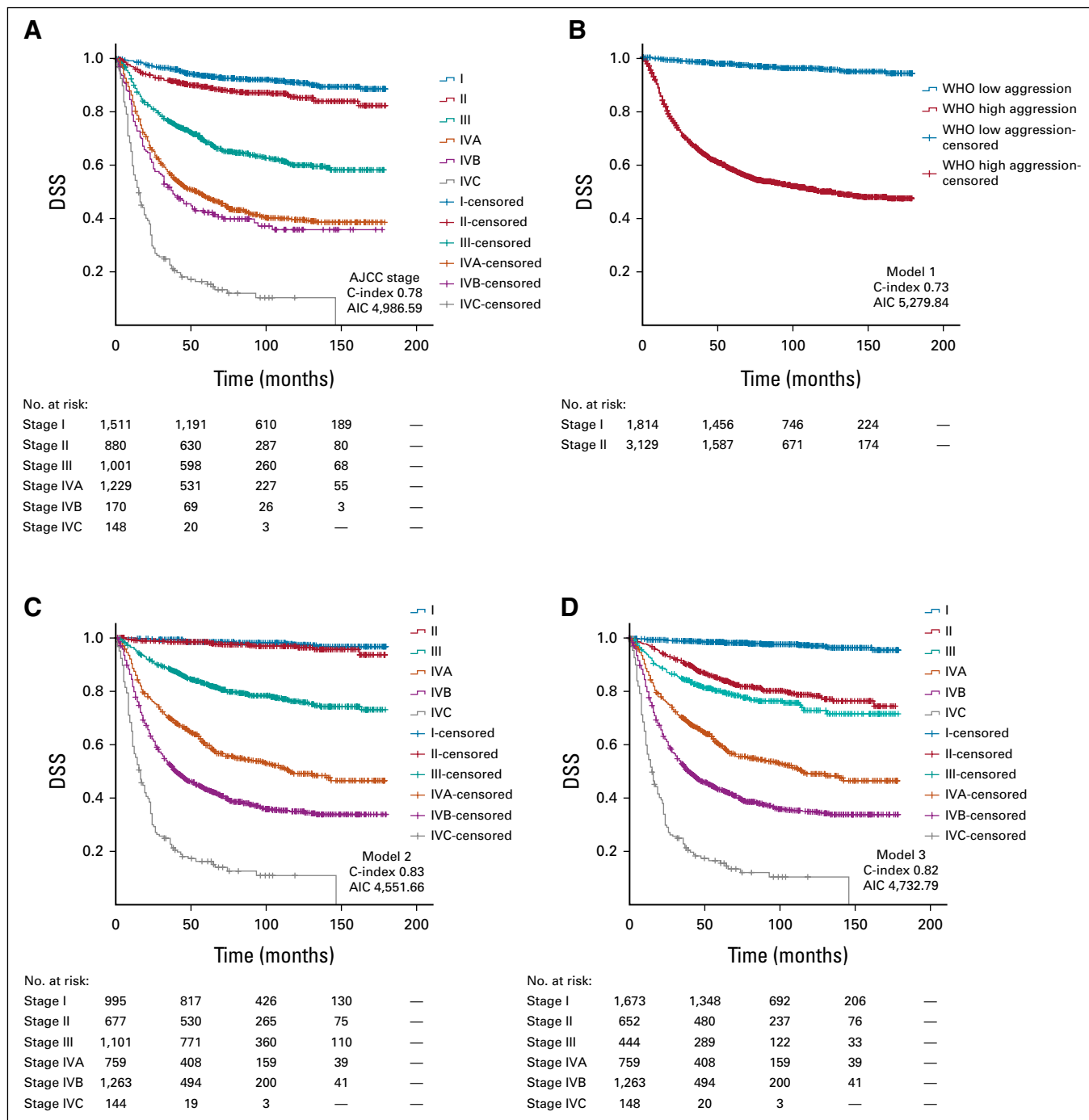


FIG 4. Kaplan-Meier plots (DSS With 95% CIs) in development cohort (A) based on Current AJCC (8th ed) staging system, (B) based on Model 1 staging system, (C) based on Model 2 staging system, (D) based on Model 3 staging system, and (E) based on Model 4 staging system. AIC, Akaike Information Criterion; AJCC, American Joint Cancer Committee; C-index, concordance index; DSS, disease-specific survival.

cohort was divided into low aggression (56%) and high aggression (44%) based on tumor histology and grade of tumor. Both the cohorts were comparable in terms of covariates (Table 1). At 63 months, the baseline hazard for OS and DSS of this cohort was 0.234 (SD 0.027) and 0.181 (SD 0.025) respectively. Figure 5 shows the OS and DSS curves for AJCC staging and Model 4 of the

candidate staging system. Model 4 performed better than other staging systems with lower AIC (222.47), higher C-index (0.81 with SD of 0.032), better calibration and better stratification of patients into distinct prognostic groups (Figs 3 and 5). Table 3 summarizes the stage migration from AJCC 8th edition to our proposed staging system in SEER database cohort.

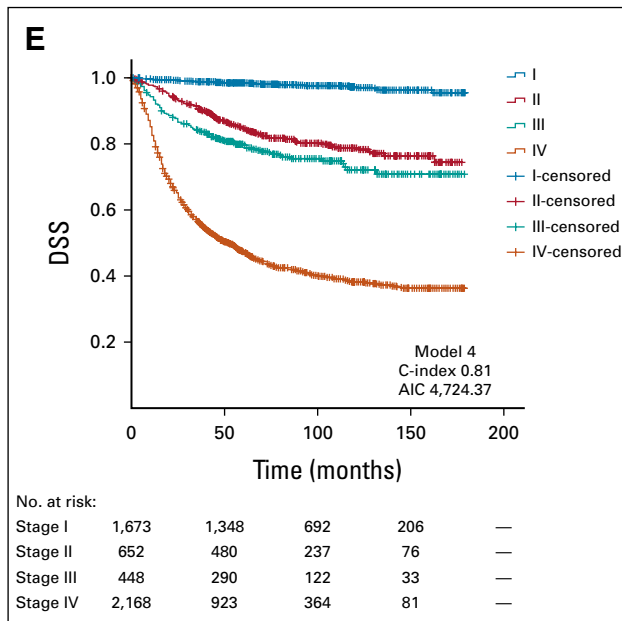


FIG 4. (Continued).

Calibration plots (Fig 3) also suggest that the model has good calibration in both cohorts as suggested by slope and R^2 values.

DISCUSSION

Our analysis shows the importance of including grade and histology in the current staging AJCC system for better stratification (Fig 2). Similar results in the external validation cohort lends credence to our concept of including tumor grade and histology in the staging of salivary gland tumors (Fig 4). Multiple studies have shown that tumor grade i.e. high grade histology is a significant predictor for survival.^{3,4}

The main aim of any staging system is better stratification of patients into groups and to discriminate the hazard of death due to the disease. The current AJCC system for salivary gland malignancies to an extent does these two things. But it does not take grade and histology of the tumor into account. The major reason for this is the variation in reporting and grading of salivary gland tumors.⁵ This is compounded by the fact that the benign tumors tend to have extracapsular spread and other signs of malignancy while on the other hand malignant tumors can present as well encapsulated especially in early stage leading to confusion in reporting.

The current WHO 2017 classification of salivary gland tumors⁶ aims to streamline reporting with a less complex system of classification. In addition to various criterias and reporting guidelines, usage of immunohistochemistry has resulted in better reporting quality and lesser variability. Hence, we realized the need for including tumor grade and histology into the current staging to improve the stratification of tumors. Instead of looking at impact of grade and histology separately on survival, we combined the two

factors resulting in two groups as per risk stratification used in WHO 2017 classification based on grade and type of histology into “Low Aggression” and “High aggression” groups.¹ This will make the classification simpler while retaining both grade and histology in it.

As salivary gland malignancies remain a surgical disease, we have included only those patients who were managed surgically. This resulted in a homogenous cohort of patients using which we were able to generate a model of predictors. In agreement with prior studies, we found that histology and grade is an independent predictor of OS and DSS in multivariable analyses. Regression model retaining only the variables with highest correlation (histological risk stratification and stage) after removal of variables with multicollinearity (grade, age, sex and M1 status) resulted in good prediction of outcome. Moreover, this model resulted in an improved fit without decreasing predictive capacity of the model. Based on these, we generated four candidate staging systems that modify the existing AJCC category by incorporating histological risk stratification (Table 2).

Importantly, the association between AJCC stage with OS and DSS and remained significant after controlling for grade and histology, suggesting that they provide complementary information (Fig 2). Model 4 was preferred based on relative simplicity, lower AIC, higher C-index, better stratification of patients into distinct prognostic groups with well separated curves on visual inspection and minimal overlap of 95% CIs for OS (Fig 2) and DSS (Fig 4).

However, the tremendous variability and frequent lack of clarity regarding reporting of histology and grades especially, needs to be understood. Each histological subtype in salivary gland tumors have different grading systems that have been proposed. For example, mucoepidermoid carcinoma has multiple systems for grading them into different classes in a twice a day to prognosticate the tumors. The grading systems are namely the modified Healy system,⁷ Armed Forces Institute of Pathology system,⁸ Brandwein system⁹ and Katabi system.¹⁰ The main issues with the grading systems are the inconsistency in the reporting and same tumor getting different grades in different systems.¹¹ Adenoid cystic carcinoma is graded by Perzin¹²—Szanto system¹³ and by Spiro system.¹⁴ Again, inter observer agreement was quite low and reproducibility was good only for solid component as demonstrated by Therikildsen et al.¹⁵ The introduction of Milan system¹⁶ has resulted in standardization of reporting in salivary gland tumors. Since the Milan system was proposed, several studies^{17,18} have shown its diagnostic utility by examining the risk of malignancy for each category of the system. This has also resulted in better reproducibility of results across all levels of experience¹⁹ and reduced cyto-histological discordance (11.7% by Rohilla et al²⁰). Hence, we can expect better concordance in reporting of these tumors due to these improvements.

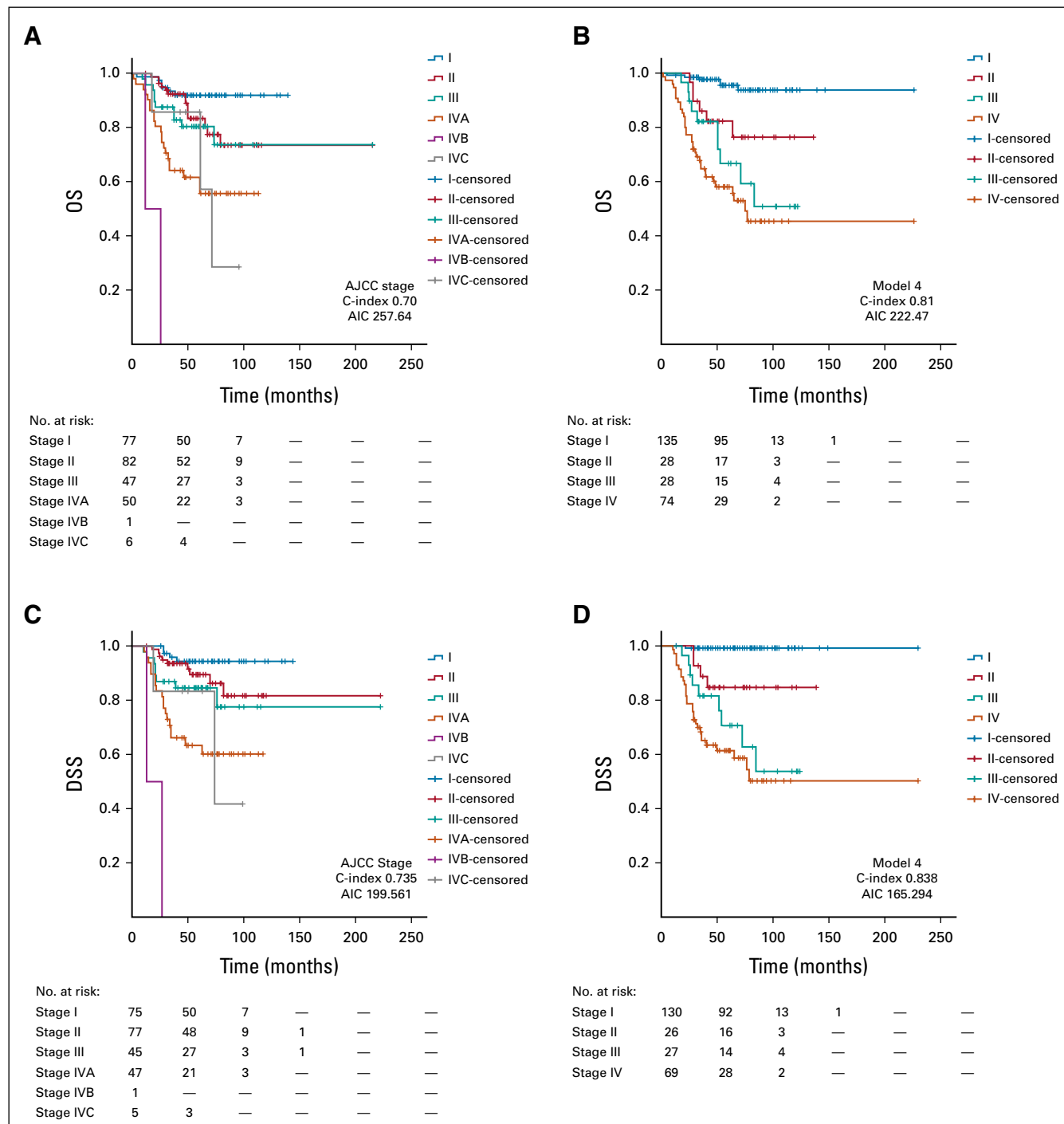


FIG 5. Kaplan-Meier Plots (OS and DSS with 95% CIs) for validation cohort. (A) Kaplan-Meier plots (OS with 95% CIs) based on Current AJCC (8th ed) staging system. (B) Kaplan-Meier plots (OS with 95% CIs) based on Model 4 staging system. (C) Kaplan-Meier plots (DSS with 95% CIs) based on Current AJCC (8th ed) staging system. (D) Kaplan-Meier plots (DSS with 95% CIs) based on Model 4 staging system. AIC, Akaike Information Criterion; AJCC, American Joint Cancer Committee; C-index, concordance index; DSS, disease-specific survival; OS, overall survival.

Unlike previous studies that have looked at incorporating grade and histology in staging of salivary gland tumors,²¹ we have used a combination of both of these factors and categorized tumors into low and high aggression as described in ASCO guidelines.¹ We believe that this categorization will

result in better stratification of tumors prognostically and also holds the advantage of ease of usage in the clinic.

As the performance of prediction models is generally poorer in new patients than in the development population, models should not be recommended for clinical use before

TABLE 3. Stage Migration (SEER database)

AJCC 8th edition	Proposed Staging System (Model 4)			
	Stage I	Stage II	Stage III	Stage IV
Stage I (n = 1,758)	1,112 (63.3%)	646 (36.7%)	—	—
Stage II (n = 1,117)	512 (45.8%)	—	605 (54.2%)	—
Stage III (n = 1,336)	271 (20.3%)	—	—	1,065 (79.7%)
Stage IV a (n = 1,652)	—	140 (8.5%)	—	1,512 (91.5%)
Stage IV B (n = 187)	—	23 (11.1%)	—	184 (88.9%)
Stage IV C (n = 176)	—	—	5 (2.8%)	171 (97.2%)

Abbreviation: AJCC, American Joint Cancer Committee.

external validity is established.² Hence, we validated our results based on SEER database on our hospital database which was from a completely different population cohort (Table 1). Model 4 performed well in the external database with good hazard discrimination (Fig 5).

Key strengths of our study are (1) use of a large population database for model generation, (2) use of objective statistical methods in choosing the best model, (3) use of a combined aggression grouping including both histological grade and type unlike previous studies and nomograms,^{21,22} (4) use of appropriate statistical measures for discrimination and calibration of models, (5) independent external validation in a distinct population cohort and (6) use of validated Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis guidelines for reporting. Our study also has its limitations like (1) records related to prognosis, such as lymphovascular invasion, margins, perineural invasion, tobacco/alcohol use, adjuvant therapy and targeted therapy were inaccessible in the SEER database, (2) details regarding extra nodal extension, molecular rearrangements were not available, (3) wrong data entry, missing data, (4) study was performed using a combination of prospectively and

retrospectively collected data with lack of randomised treatment allocation, (5) variability in reporting of histology and grade of tumor and (vi) lack of adjuvant therapy data and resulting variability in their use due to lack of consensus guidelines.

In conclusion, our results show that combination of tumor grade and histology is an independent predictor of OS and DSS in salivary gland tumors and provides additional prognostic information along with AJCC category. We propose a modification that incorporates these two factors that improved discrimination among patient subgroups with respect to both OS DSS when compared with the current AJCC staging system. This staging system can be easily implemented in clinical practice as we have externally validated the model. However, consensus on definition of grades and histological reporting needs to be formulated to ensure reproducibility across all centers and facilitate accurate comparisons between institutions. Also, conducting further studies incorporating lymphovascular extension, perineural invasion, margins, nodal status, molecular markers and adjuvant therapy is imperative in order to fine tune our proposed staging system for better prognostication.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.

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