Machine Learning vs Traditional Statistics: Developing a Novel Proxy for HPV-associated LA SCCHN

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Background

- HPV is a strong prognostic factor for survival in LA SCCHN and valuable for risk stratification
- Existing proxies for predicting HPV status in LA SCCHN are inaccurate and unreliable[1,2]

Study Objectives

- To identify a better performing proxy for HPV status
- Compare the performance of traditional statistical vs machine learning methods

Methods

- Database: SEER Incidence Database - Head and Neck with HPV Status Database (2010-2017) with Census Tract-level SES/Rurality
- Timeframe: 2010-2017
- Inclusion Criteria: 1) LA (locally advanced) (AJCC stage III-IVB), 2) Oropharynx squamous cell carcinoma, 3) Age 18 or older
- Exclusion Criteria: 1) Missing HPV status, 2) Missing data on covariates
- Predictor variables: All available pre-treatment patient characteristics:
  - Sex, Age, Race/ethnicity, national Yost socio-economic status index quintiles, marriage status, urbanicity, year of diagnosis, tumor involvement, node involvement,
- Data Split: Training (80%), Test (20%)
- Models: logistic regression, stepwise logistic regression, LASSO, elastic net, stepwise elastic net, random forest, GBM, XGBoost
- Hyperparameter tuning was performed for ML models
- Base case thresholds for ML models were chosen by maximizing sensitivity & specificity, scenario analysis thresholds were chosen by minimizing cost, where a false positive was 4x more costly than false negative

Table 1. Patient attrition

Description of step	n	% of previous step retained
Patients in SEER Research Plus, Head and Neck with HPV Status and Census Tract-level SES/Rurality Combined Database (2006-2018)	5,531,627	100%
Patients diagnosed from 2010-2017	3,464,655	62.6%
Patients in SEER Research Plus, 21 registries, Nov 2020 Sub (2000-2018) with malignant tumors and known age	107,936	3.1%
With TNM staging available from the derived AJCC, 7th edition (2010-2015) or derived SEER combined stage (2016-2017)	105,019	97.3%
Patients with tumors in oral cavity, oropharynx, larynx, or hypopharynx sites	94,923	90.4%
Patients with tumors only in Oropharynx site	36,128	38.1%
Patient has HPV Positive or HPV Negative status	19,489	53.9%
Patients with AJCC7 staging III or IVA/B (HPV- or HPV+) SCCHN involving oropharynx	15,115	77.6%
Patients 18 years or older	15,113	99.9%
Patients without missing data for all explanatory variables (race/origin, SES, marital status, urban/rural status)	13,645	90.3%

Results

Table 2. Patient Characteristics

Characteristics	N = 13,645
Female n (%)	2,032 (14.9%)
Age in years: mean (SD)	60.96 (9.90)
Race n (%)	
•Non-Hisp American Indian/ Alaska Native	70 (0.5%)
•Non-Hisp Asian/Pacific Islander	377 (2.8%)
•Non-Hisp Black	1,028 (7.5%)
•Non-Hisp White	11,280 (82.7%)
•Hispanic (all races)	890 (6.5%)
SES n (%)	
•Group 1 (lowest SES)	1,796 (13.2%)
•Group 2	2,037 (14.9%)
•Group 3	2,373 (17.4%)
•Group 4	3,136 (23.0%)
•Group 5 (highest SES)	4,303 (31.5%)
Urban vs Rural n (%)	
•All Urban	8,689 (63.7%)
•All Rural	893 (6.5%)
•Mostly Urban	3,052 (22.4%)
•Mostly Rural	1,011 (7.4%)
Year of Diagnosis n (%)	
•2010	621 (4.6%)
•2011	972 (7.1%)
•2012	1,309 (9.6%)
•2013	1,668 (12.2%)
•2014	1,926 (14.1%)
•2015	2,104 (15.4%)
•2016	2,460 (18.0%)
•2017	2,585 (18.9%)
Tumor Size n (%)	
•T0	69 (0.5%)
•T1	3,529 (25.9%)
•T2	4,900 (35.9%)
•T3	2,734 (20.0%)
•T4	2,348 (17.2%)
•TX	65 (0.5%)

Characteristics	N = 13,645
Marriage Status n (%)	
•Married (including common law)	8,408 (61.6%)
•Divorced	1,834 (13.4%)
•Separated	170 (1.2%)
•Single (never married)	2,485 (18.2%)
•Unmarried or domestic partner	98 (0.7%)
•Widowed	650 (4.8%)
Urban vs Rural n (%)	
•All Urban	8,689 (63.7%)
•All Rural	893 (6.5%)
•Mostly Urban	3,052 (22.4%)
•Mostly Rural	1,011 (7.4%)
Node Score n (%)	
•N0	900 (6.6%)
•N1	2,552 (18.7%)
•N2	9,506 (69.7%)
•N3	680 (5.0%)
•NX	7 (0.1%)
Metastasis Score n (%)	
•M0	13,645 (100%)
SES n (%)	
•Group 1 (lowest SES)	1,796 (13.2%)
•Group 2	2,037 (14.9%)
•Group 3	2,373 (17.4%)
•Group 4	3,136 (23.0%)
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Table 3. Performance of predictive models for HPV-associated LA SCCHN

Threshold chosen by maximizing sensitivity and specificity (F1 score)

	Threshold	Sensitivity	Specificity	NPV	PPV	Test AUC †
Proxy 1 (All HPV+)	NA	1.000	Undefined	Undefined	1.000	0.000
Proxy 2 (Oropharynx site, young (<65), white, male)	NA	0.507	0.643	0.300	0.812	0.556
Logistic Regression	0.76	0.690	0.637	0.403	0.853	0.719
Stepwise Logistic Regression	0.78	0.628	0.679	0.375	0.856	0.720
Lasso*	0.76	0.683	0.636	0.397	0.851	0.720
Elasticnet*	0.76	0.682	0.637	0.396	0.851	0.721
Stepwise Elasticnet*	0.78	0.620	0.688	0.373	0.858	0.721
Random Forest*	0.78	0.597	0.709	0.366	0.862	0.718
GBM*	0.78	0.628	0.690	0.378	0.860	0.722
XGBoost*	0.77	0.643	0.675	0.383	0.858	0.723

*: Hyperparameter tuning for these models were performed using 5-fold cross-validation

†: Test AUC was calculated using test dataset, separate from the training dataset

AUC = Area under ROC curve (measures model's ability to discriminate between two classes). For example, AUC of .72 means 72% of HPV+ patients have correctly higher P(HPV+)

Figure 1. Impact of variables on predicted HPV status (XGBoost Model)

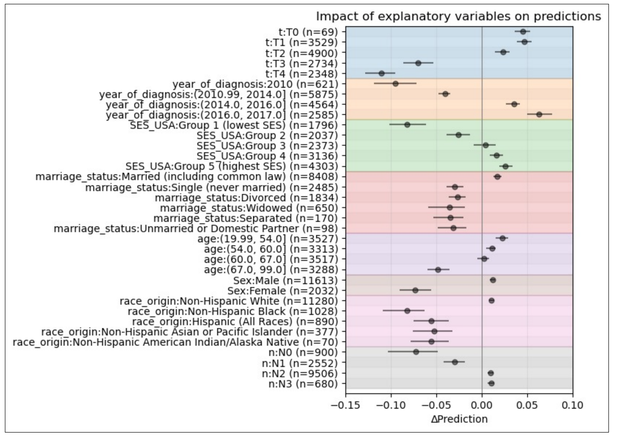
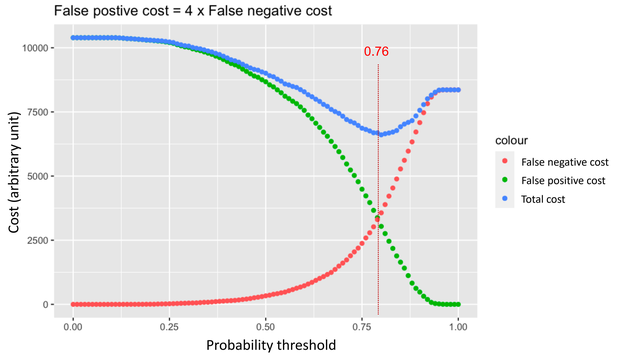


Figure 2. Threshold selection for scenario analysis of "cost" minimization



Note: Y-axis cost units are arbitrary, as the costs of FN/FP would yield identical results as long as FP = 4x FN costs. Threshold was chosen using the probability at which "cost" was lowest.

Table 4. Performance of predictive models for HPV-associated LA SCCHN

(Scenario analysis using threshold chosen by minimizing "cost")

	Threshold	Sensitivity	Specificity	NPV	PPV	Test AUC †	Relative Cost
Proxy 1 (All HPV+)	NA	1.000	Undefined	Undefined	1.000	0.000	130.7%
Proxy 2 (Oropharynx site, young (<65), white, male)	NA	0.507	0.643	0.300	0.812	0.556	100%
Logistic Regression	0.82	0.690	0.637	0.403	0.853	0.719	81.8%
Stepwise Logistic Regression	0.80	0.628	0.679	0.375	0.856	0.720	82.5%
Lasso*	0.79	0.683	0.636	0.397	0.851	0.720	82.7%
Elasticnet*	0.78	0.682	0.637	0.396	0.851	0.721	82.6%
Stepwise Elasticnet*	0.80	0.620	0.688	0.373	0.858	0.721	82.0%
Random Forest*	0.78	0.597	0.709	0.366	0.862	0.718	81.6%
GBM*	0.80	0.628	0.690	0.378	0.860	0.722	81.0%
XGBoost*	0.79	0.591	0.715	0.365	0.863	0.723	81.4%

Discussion and limitations

- We were unable to take full advantage of our ML methods due to low number of covariates
- Missing important variables such as smoking & alcohol history, geographic info, HPV risk-factors
- No data if patient receives care in non-SEER region (reducing generalizability)
- Exclusion of patients with missing data could have biased results

Conclusions and recommendations

- Both ML models and logistic regression-based methods outperformed existing proxy methods for identifying HPV associated LA SCCHN
- ML performed similarly to logistic regression in this limited dataset
- ML may further outperform traditional statistics in datasets with larger number of covariates & patients as ML uniquely characterizes non-linear relationships between variables
- Learnings from the methods & interpretation of this analysis can be applied in future predictive models & HEOR analyses

Abbreviations

AJCC: American Joint Committee on Cancer; AUC: Area under the curve; GBM: Gradient-boosting machine; HPV: Human papillomavirus; LA: locally advanced; LASSO: Least Absolute Shrinkage and Selection Operator; ML: Machine learning; NPV: Negative predictive value; PPV: Positive predictive value; SCCHN: Squamous cell carcinoma of the head and neck; SEER: Surveillance, Epidemiology, and End Results; SES: Socio-economic status; SHAP: SHapley Additive exPlanations; XGBoost: Extreme Gradient Boosting

References

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2. Cancer. 2019;125(2):249-260. doi:10.1002/cncr.31800

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