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Early and late mortality among patients with T1–T3 head and neck squamous cell carcinoma: a machine learning analysis using a SEER population-based cohort study

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Despite advances in the management of head and neck squamous cell carcinoma (HNSCC), mortality within 6 months of diagnosis remains a substantial clinical challenge. The objectives of this study are: (i) to develop a machine learning (ML) model using data from the Surveillance, Epidemiology, and End Results (SEER) program to assess the influence of patient characteristics, tumor features, and treatment modalities on early mortality in HNSCC; (ii) to explore and compare the prognostic potentials of patient-, tumor, and treatment-related factors across distinct mortality time points—6-month mortality (early mortality), 24-month mortality, and 5-year mortality; and (iii) to externally and independently validate the early mortality model using multicenter data from the Thuringian Cancer Registry (Jena, Germany) and a prospective observational cohort from the Helsinki University Hospital (Helsinki, Finland). We identified 4802 patients with HNSCC from the SEER for model development. Permutation-based feature importance was used to identify risk factors associated with early mortality. External validation was conducted using 1952 cases from the Thuringian Cancer Registry and 58 cases from the Helsinki University Hospital. The ML model achieved a weighted area under curve (AUC) of 0.75 for predicting early mortality in the SEER cohort. External validation yielded weighted AUC values of 0.70 (Germany) and 0.60 (Finland). Aggregate feature importance for early mortality indicated that higher age at diagnosis, presence of earlier primary malignant tumors besides HNSCC, unmarried patients with T1–T3 HNSCC, T3 stage, and having hypopharyngeal or laryngeal cancer, in decreasing order of significance, were important. For 24-month mortality, the associated risk factors in decreasing order of significance were T3 stage, being elderly in terms of age at diagnosis, presence of earlier primary malignant tumors besides HNSCC, having hypopharyngeal or oral cavity cancer, and N3 stage. The associated risk factors for 5-year mortality were found to be the same with those of early mortality with the additional inclusion of T2 stage. Identification of patients at elevated risk of early death supports timely intervention and individualized therapeutic decision-making. The developed ML

model identified several risk factors associated with early death and may aid in clinical decision-making with the potential to improve survival outcomes.

Keywords Machine learning, Head and neck squamous cell carcinoma (HNSCC), Head and neck cancer (HNC), Overall survival, Early mortality, SEER, Surgery, Radiotherapy, Chemoradiotherapy

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Head and neck cancer (HNC) is among the ten most common malignancies globally and is frequently diagnosed at advanced stage, which typically results in decreased overall survival (OS)[1,2]. Incidence rates of HNC vary across geographic regions and are influenced by tumor-specific parameters, including anatomic subsite and histology. In the United States, for example, between 2022 and 2024, there were 54,000 new cases and more than 11,230 deaths from the disease[3–5]. Globally, according to the GLOBOCAN 2022 report, HNC accounted for 947,000 new cases and 482,000 deaths[6]. This represents roughly 4.5% of all cancer diagnoses globally and about 4.6% of cancer deaths[7,8]. Approximately 90% of all HNC cases are squamous cell carcinomas (HNSCCs)[5,9]. The incidence of HNSCC has been projected to rise to approximately 1 million by 2030[8,10].

Even after successful treatment, patients with HNSCC remain at high risk of disease recurrence, especially loco-regional recurrence, and cancer-related mortality[11]. While treatment for most patients has been given with curative intent aimed at long-term survival, sizeable number of these patients experience early death within 6 months after diagnosis or treatment (early mortality)[9,12]. Early mortality may arise from tumor-related factors, patient-specific comorbidities, and treatment-related toxicities or perioperative complications[2]. Although estimates vary across cohorts, early mortality rates ranging from 3% to 11% have been reported[9,12–15]. Despite the sizeable number of patients in this subgroup, few studies have rigorously examined this topic in population-based epidemiologic settings[2,9,14,16,17]. Most of these studies have primarily focused on a narrow range of clinical factors, such as tumor stage and site, and treatment methods[9]. The current study extends this approach by combining patient-, tumor-, and treatment-related factors to predict early mortality in this subgroup. Early prediction of patients with early mortality may aid in optimizing treatment strategies[9].

However, predicting early death in HNSCC remains challenging even for experienced clinicians. HNSCCs are presented at advanced stage when the disease has the potential to spread extensively and invade vital anatomical structures[18]. As such, the prognosis is poor, and the cause of death may be predominantly due to tumor progression[18]. Therefore, it is imperative to understand the factors responsible for death, not only early death (at 6 months) but also at a later time points, since the survival range for advanced HNSCC range between 23 and 43 months depending on treatment and individual factors[18,19]. Therefore, this period represents a crucial time for patients with HNSCC as many will develop a locoregional recurrence[20,21]. Likewise, from a clinical perspective, the first 5 post-treatment years of HNSCC are usually considered to be vital since most recurrences and deaths from HNSCC occur within that time frame[22].

Owing to these, a prediction model or risk assessment score could serve as a valuable adjunct for identifying patients at high risk of early death, as well as for predicting mortality at subsequent time points such as 24 months and 5 years. Such tools may support personalized treatment adjustments, facilitate informed decision-making, optimize resource allocation, and ultimately contribute to improved OS and overall management of HNC. Prior knowledge of such risk could facilitate a transition from one-size-fits-all approaches to targeted individualized interventions that avoid unnecessary procedures and prioritize strategies maximizing both life expectancy and quality of life.

Given the promising performance of machine learning (ML) methods in oncology in recent years[23–26], this study proposes to investigate the utility of ML for predicting early mortality in HNSCC. This study has three objectives: (i) to develop an ML model—a subfield of artificial intelligence—using data from the Surveillance, Epidemiology, and End Results (SEER) Program to evaluate the influence of patient characteristics, tumor features, and treatment modalities on early mortality in HNSCC; (ii) to explore and compare the prognostic potentials of patient-, tumor-, and treatment-related factors across distinct mortality time points—6-month mortality (i.e., early mortality), 24-month mortality, and 5-year mortality; and (iii) to externally and independently validate the early mortality model (objective i) using multicenter data from the Thuringian Cancer Registry (Jena, Germany) and a retrospective observational cohort from the Helsinki University Hospital (Helsinki, Finland). We compared early mortality with the two other time points (objective ii) because a considerable portion of HNSCC patients (~ 34%) are likely to die within five years of diagnosis[2,27,28] despite substantial therapeutic advances over recent decades[29]. The proposed model is intended as an ancillary clinical tool to identify patients at heightened risk of early mortality, enabling timely and targeted treatment planning aimed at improving survival and quality of life, and avoiding unnecessary radical interventions. This will further reduce economic burden on patients, families, and healthcare systems. While most prior investigations have focused predominantly on OS in HNSCC, to the best of our knowledge, this is the first population-based study to develop and validate an ML-driven model for mortality prediction at three time points, with a specific emphasis on 6-month mortality, and to systematically

analyze the contributions of patient-, tumor-, and treatment-related factors to early death in HNSCC. Of note, literature employs diverse definitions of early mortality. In this study, we adopt a 6-month threshold, consistent with prior research by our group[9] and other studies[12,14,30].

Materials and methods

Patient selection

This study utilized SEER*Stat software (version 9.0.41.4; https://seer.cancer.gov/SEER) to access population-based cancer registry data[31]. Specifically, the Incidence—SEER Research Plus Data, 8 Registries, Nov 2024 Submission (1975–2022) was employed[31]. HNC cases were identified within SEER using International Classification of Diseases (ICD) coding consistent with ICD-O-3/WHO 2028 for site and morphology (Fig. 1).

Following HNC case identification, inclusion criteria were: (i) histologically confirmed HNSCC; (ii) availability of comprehensive clinicopathological and follow-up information; and (iii) known survival or alive status, and (iii) documented survival time. Exclusion criteria were: (1) unknown cases in any variables selected for analysis, for example, race ($n = 34$), marital status ($n = 548$), grade ($n = 1206$), and (2) other tumor sites different from HNSCC. The detailed description of the selected variables is detailed in "Selection of patient attributes", and the corresponding unknown cases removed are presented in Supplementary 1. We also excluded HNSCC sites with low patient numbers, including the nasopharynx and sinonasal regions, and T4 stage as the small sample sizes were insufficient to draw meaningful conclusions in this study. Moreover, as treatment intent was not specified in the SEER database and the objective of the study was to evaluate patients treated with curative intent, we excluded all cases presumed to have been addressed with palliative treatment (i.e. patients who received no treatment or chemotherapy alone). A detailed patient selection workflow is shown in Fig. 1. After excluding patients with incomplete information, a total of 4802 patients with HNSCC were enrolled in the study.

Selection of patient attributes

Due to inherent limitations of the SEER database, the analytical variables were restricted to three principal domains: patient demographic, clinicopathologic, and treatment parameters. Demographic variables comprised age at diagnosis, sex, race, and marital status. Clinicopathologic variables included primary tumor site, tumor–node–metastasis (TNM) stage as defined by the American Joint Committee on Cancer (AJCC) 7th edition staging system, histological grade of HNSCC, and first primary tumor indicator (i.e. HNSCC is the first cancer diagnosis of the patient). Treatment-related variables encompassed surgical intervention, radiotherapy, and chemoradiotherapy (Table 1).

All the methods were performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. The detailed description of all the cases extracted, as shown in Fig. 2, is presented in Table 1. Table 1 shows the basic demographic characteristics of the HNSCC patients extracted from the SEER database. Additionally, it shows the distribution of the three considered mortality time points. The outcome of interest was the overall survival status (alive or dead) of HNSCC patients. We also extracted the follow-up time in months for all the patients.

Ethics approval and consent to participate

Special ethical approval and consent to participate are not applicable to our study. This declaration is in line with what has been prescribed in the study on utilizing the SEER data[32]. Additionally, data use agreement containing the required ethical permission and associated details have been approved for the first author through the SEER*Stat program of the NIH Ethics Committee, United States of America. SEER is one of the largest cancer databases that are available publicly (The URL of the database is https://seer.cancer.gov/). It gives

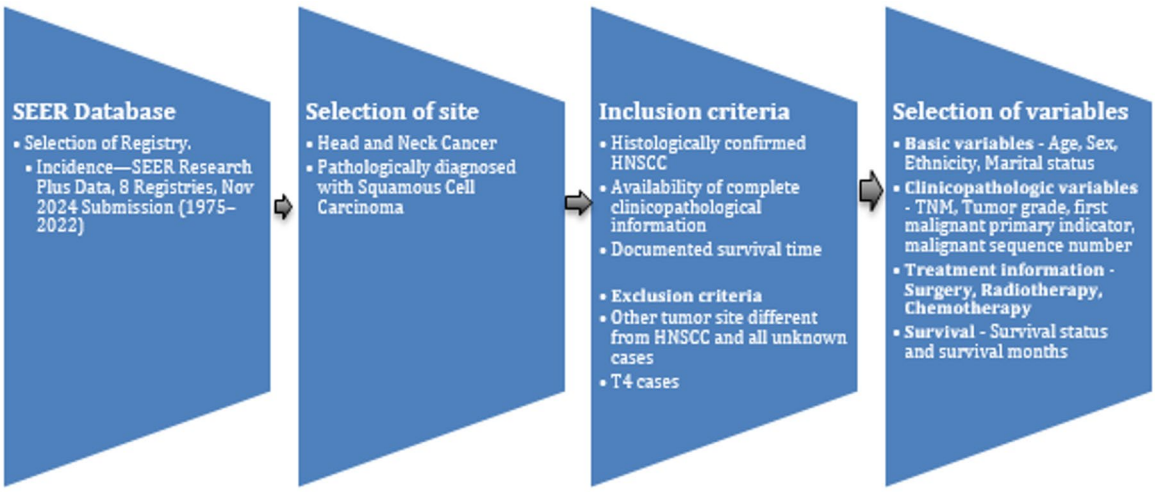

Fig. 1. Inclusion and exclusion criteria from the SEER data extraction.

Variables	Early mortality ($N=4802$)	24-month mortality ($N=4613$)	5-year mortality ($N=3957$)	ML model categorization
Age at diagnosis				
≤ 40 years old	201 (4.2%)	198 (4.3%)	178 (4.5%)	No categorization used in model development
> 40 years old	4601 (95.8%)	4415 (95.7%)	3779 (95.5%)	
Sex				
Female	1681 (35.0%)	1619 (35.1%)	1413 (35.7%)	0 = Female
Male	3121 (65.0%)	2994 (64.9%)	2544 (64.3%)	1 = Male
Race				
Black	210 (4.4%)	196 (4.3%)	164 (4.1%)	0 = Black
White	4143 (86.3%)	3978 (86.2%)	3422 (86.5%)	1 = White
Others (American Indian/Alaska Native, Asian/Pacific Islander)	449 (9.4%)	439 (9.5%)	371 (9.4%)	2 = Others
Marital status				
Married	2865 (59.7%)	2773 (60.1%)	2431 (61.4%)	1 = Married
Unmarried	1937 (40.3%)	1840 (39.9%)	1526 (38.6%)	0 = Unmarried
First primary indicator (HNSCC being the first tumor)				
No	1286 (26.8%)	1209 (26.2%)	971 (24.5%)	No = 0
Yes	3516 (73.2%)	3404 (73.8%)	2986 (75.5%)	Yes = 1
Histopathological grade				
Well differentiated, Grade I	1178 (24.5%)	1147 (23.8%)	1038 (26.2%)	1 = Grade I
Moderately differentiated, Grade II	2483 (51.7%)	2386 (51.7%)	2026 (51.2%)	2 = Grade II
Poorly differentiated, Grade III	1108 (23.1%)	1049 (22.7%)	866 (21.9%)	3 = Grade III
Undifferentiated (Anaplastic), Grade IV	33 (0.7%)	31 (0.7%)	27 (0.7%)	4 = Grade IV
Tumor site				
Lip	433 (9.0%)	419 (9.1%)	377 (9.5%)	Lip = 1
Oral cavity	3143 (65.5%)	3029 (65.7%)	2578 (65.2%)	Oral cavity = 2
Oropharynx	637 (13.3%)	616 (13.4%)	559 (14.1%)	Oropharynx = 3
Hypoparynx	97 (2.0%)	91 (2.0%)	66 (1.7%)	Hypoparynx = 4
Larynx	492 (10.3%)	458 (9.9)	377 (9.5%)	Larynx = 5
T stage				
T1	2737 (57.0%)	2667 (57.8%)	2374 (60.0%)	T1 = 1
T2	1533 (31.9%)	1467 (31.8%)	1225 (31.0%)	T2 = 2
T3	532 (11.1%)	479 (10.4%)	358 (9.0%)	T3 = 3
N stage				
N0	3818 (79.5%)	3689 (80.0%)	3208 (81.1%)	N0 = 0
N1	855 (17.8%)	807 (17.5%)	657 (16.6%)	N1 = 1
N3	129 (2.7%)	117 (2.5%)	92 (2.3%)	N3 = 3
M stage				
M0	4770 (98.3%)	4590 (99.5%)	3943 (99.6%)	M0 = Absent
M1	32 (0.7%)	23 (0.5%)	14 (0.4%)	M1 = Present
Treatment				
Surgery (Sx) alone	2989 (62.2%)	2857 (61.9%)	2506 (63.3%)	1 = Sx
Radiotherapy (RT) alone	40 (0.8%)	38 (0.8%)	32 (0.8%)	1 = RT
Chemoradiotherapy (CRT) alone	139 (2.9%)	132 (2.9%)	112 (2.8%)	1 = CRT
Sx + RT	996 (20.7%)	972 (21.1%)	809 (20.4%)	
Sx + CT	38 (0.8%)	32 (0.7%)	19 (0.5%)	
All treatment modalities (Sx + RT + CT)	600 (12.5%)	582 (12.6%)	479 (12.1%)	
Overall survival	Early morality	24-month mortality	5-year mortality	
Alive after the time points	4626 (96.3%)	3991 (86.5%)	3221 (81.4%)	0 = Alive at the end of follow-up
Dead during the time point under consideration	176 (3.7%)	622 (13.5%)	736 (18.6%)	1 = Dead of this cancer or other causes at the specific timepoints examined

Table 1. Demographic characteristics of patients with HNSCC across the three time points extracted from the SEER database ($N=4802$).

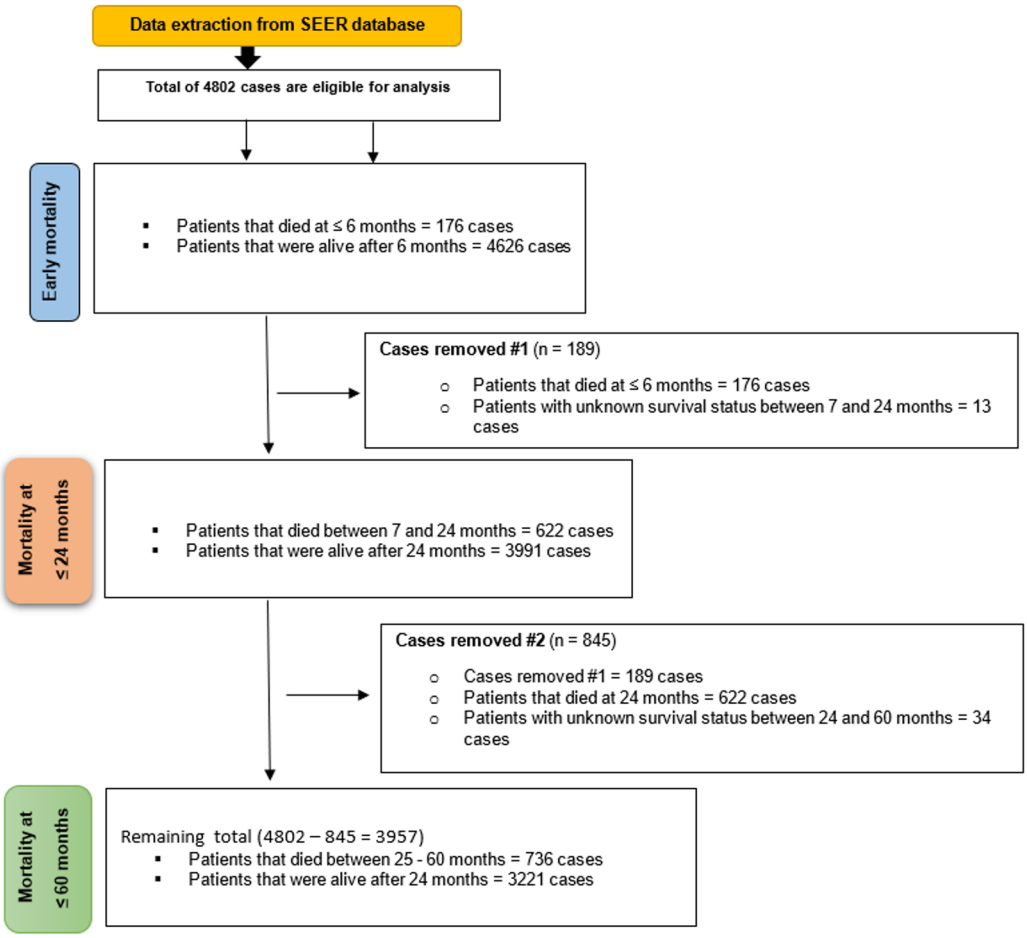

Fig. 2. Data extraction process from the SEER database (Supplementary Selection of patient attributes).

Performance accuracy	Early mortality	24-month mortality	5-year mortality
Accuracy	0.70	0.86	0.82
Weighted_AUC	0.77	0.72	0.73
Balanced accuracy	0.70	0.51	0.60
Mathews coefficient	0.39	0.10	0.20
Recall	0.64	0.04	0.12
Precision	0.70	0.28	0.60

Table 2. ML model performance at three different timepoints for overall mortality.

non-identifiable information on cancer statistics of the United States population. As a result, informed consent and human subject research ethics evaluations were not required for this study. We verified that all statistical analyses were carried out in compliance with the guidelines of the SEER Program and that the data of enrolled patients was anonymous. Ethical approvals and data governance were duly observed. The Ethics Committee of Jena University Hospital approved the study (IRB No. 3204-07/11) and waived the requirement for informed consent due to its non-interventional, retrospective design and the use of anonymized data[33]. In Finland, Research Ethics Board approval was not required under national legislation for retrospective registry-based chart reviews. However, the study permission was granted by the Research Administration of the Helsinki and Uusimaa Hospital District (HUS/307/2019).

Data processing

Following the inclusion and exclusion criteria defined in "Patient selection", a total of 4802 patients were included. The description of the selected mortality timepoints (early, intermediate, and late mortality) were presented in Table 2. The extracted features ("Selection of patient attributes") were categorized for ML model development (Table 1; Column 5). For the categorization, marital status was recorded as married (including common law) or

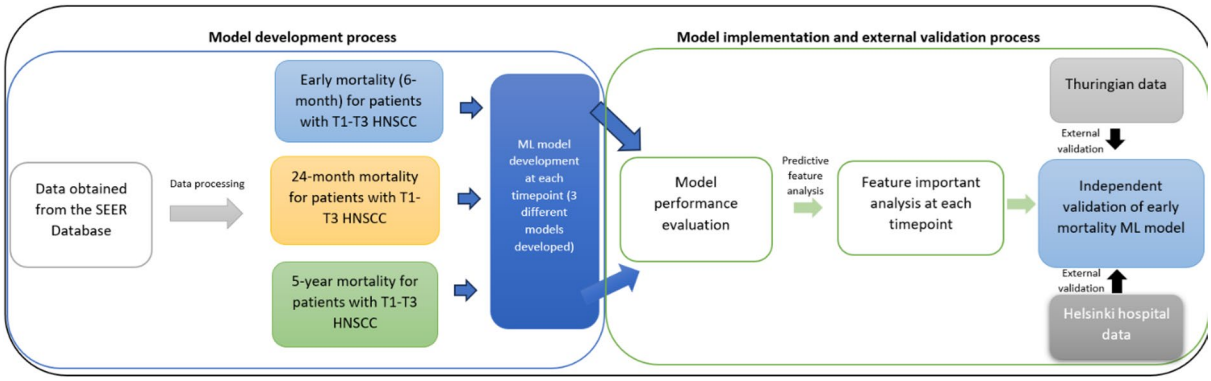

Fig. 3. The summarized model development workflow.

S/N	6-month	24-month	5-year
1	Higher T stage (T3)	Higher stage (T3)	The presence of other primary malignancy
2	Higher age at diagnosis	Tumor sites: oral cavity, hypopharynx, larynx	Higher age at diagnosis
3	Higher grade (grades III–IV)	Higher age at diagnosis	Tumor sites: oral cavity, hypopharynx, larynx

Table 3. Overview of variable importance for cancer-specific mortality at the three timepoints examined in this study.

unmarried (single, separated, divorced, and widowed). Of note, the age of the patients was used in its discrete form without categorization for the ML model development (Table 1; Column 5). This is intentional to avoid discussion around optimum threshold for the age of the patients since the age cohort of so-called "young" patients has not yet been well-defined for HNSCC[34]. Most published studies have used an age cut-off of 40–50 years[35,36]. However, for the readership of our research and to present our data concisely, we have used 40 years. Other categorization approach used for ML model development is presented in Table 1.

Machine learning model training

The model development workflow is summarized in Fig. 3. The training dataset comprised three categories of variables: (a) demographic parameters (age at diagnosis, sex, race, marital status); (b) clinicopathological and tumor characteristics (tumor site, stage, grade, and TNM staging); and (c) treatment parameters. The primary outcomes were mortality at predefined time points: 6-month (early) , 24-month, and 5-year mortality.

For each time point, three distinct ML models were trained. The curated datasets for each time point (Table 1) were imported into Azure Machine Learning Studio. After data ingestion, we specified key training configurations, including the choice of ensemble algorithms (voting and stacked ensembles), learning rate, five-fold cross-validation, and evaluation metrics. The voting ensemble paradigm, as the name implies, uses ensemble machine learning method in which multiple models based on light and extreme gradient boosting algorithms (called base learners) are combined to make a single, more accurate and more robust prediction than any individual model could achieve on its own. This approach was intended to enhance the overall performance, stability, and generalization of machine learning models by mitigating overfitting and effectively managing complex data interactions through the integration of diverse models[37,38]. In voting ensemble used in our study, the final prediction is based on the weighted average of predicted class probabilities of all the participating models (soft voting) instead of choosing the majority prediction from each participating model (hard voting)[38]. Therefore, the voting ensemble paradigm, which aggregates diverse, accurate learners, will reduce variance and error correlation, and this lead to improved generalization without increasing model complexity[38]. In stacked ensembles, on the other hand, heterogeneous models are combined to train a meta-model based on the output from the individual models. The current default meta-models for stacked ensemble use logistic regression for classification tasks as presented in our study. Hyperparameters were systematically tuned to optimize model performance. Model performance was assessed primarily using accuracy. Secondary evaluation metrics included sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC) for overall mortality at the three time points (Table 2). As a sub-analysis, we equally developed three ML models for cancer-specific mortality and performed feature importance analysis to evaluate the contribution of the input variables on cancer-specific mortality ("Cancer-specific mortality"; Table 3).

External geographic validation for the early mortality model

The early mortality ML model was externally validated using two independent cohorts: a geographic validation cohort from the Thuringian Cancer Registry (Jena, Germany) and a prospective observational cohort from the Helsinki University Hospital (Helsinki, Finland). The external validation cohorts had neither information about the marital status nor if HNSCC was the first primary. Hence, the early mortality model was retrained to

match the validation cohorts. The baseline demographic and clinical characteristics of the HNSCC patients from the Thuringian Cancer Registry and those from Helsinki University Hospital are presented in Table 4. Model performance for each time point after development is presented in Table 2 while the ML predictive performance for early mortality time point under external validation is summarized in Table 5.

Feature importance analysis

Overall survival

We employed feature importance to assess the contribution of each input variable to the ML model's prediction of 6-month (early) , 24-month, and 5-year mortality. This method evaluates importance by randomly shuffling the values of one feature at a time and measuring the resulting change in model performance. Performance is quantified using predefined metrics (e.g., accuracy) computed before and after permutation. The difference in performance reflects the extent to which the shuffled feature influences the model's predictive ability. Features

Variables	Thuringian ($N=1952$) *	Helsinki data ($N=58$) **
Age at diagnosis		
≤ 40 years old	60 (3.1%)	1 (1.7%)
> 40 years old	1882 (96.4%)	57 (98.3%)
Sex		
Female	337 (17.3%)	23 (39.7%)
Male	1615 (82.7%)	35 (60.3%)
Race		
White	1952 (100.0%)	58 (100.0%)
Histopathological grade		
Well differentiated, Grade I	292 (15.0%)	11 (19.0%)
Moderately differentiated, Grade II	1284 (65.8%)	31 (53.5%)
Poorly differentiated, Grade III	374 (19.2%)	15 (25.9%)
Undifferentiated (anaplastic), Grade IV	2 (0.1%)	1 (1.7%)
Tumor site		
Lip	122 (6.3%)	0 (0.0%)
Oral cavity	675 (34.6%)	36 (62.1%)
Oropharynx	359 (18.4%)	6 (10.3%)
Hypoparynx	113 (5.8%)	6 (10.3%)
Larynx	683 (34.9%)	10 (17.2%)
T stage		
T1	887 (44.4%)	23 (39.7%)
T2	680 (32.8%)	26 (44.8%)
T3	385 (18.6%)	9 (15.5%)
N stage		
N0	1564 (80.0%)	42 (72.4%)
N1	331 (18.1%)	13 (22.4%)
N3	57 (2.9%)	3 (5.2%)
M stage		
M0	1933 (99.0%)	57 (98.3%)
M1	19 (1.0%)	1 (1.7%)
Treatment		
Surgery (Sx) alone	848 (43.4%)	23 (39.7%)
Radiotherapy (RT) alone	67 (3.4%)	11 (19.0%)
Chemoradiotherapy (CRT) alone	62 (3.2%)	8 (13.8%)
Sx + RT	671 (34.4%)	10 (17.2%)
Sx + CT	23 (1.2%)	0 (0.0%)
All treatment modalities (Sx + RT + CT)	281 (14.4%)	6 (10.3%)
Overall survival	Early morality	
Alive after 6 months	1870 (95.8%)	44 (75.9%)
Death within 6 months	82 (4.2%)	14 (24.1%)

Table 4. Demographic and clinical characteristics of patients with HNSCC across the two geographic validation cohorts. *A subset of the Thuringian data matched to the SEER variables used for model training. **A subset of the Helsinki data matched to the SEER variables used for model training.

Performance accuracy	Early mortality		
	SEER data	Thuringian data	Helsinki data
Accuracy	0.68	0.60	0.50
Weighted_AUC	0.75	0.70	0.60
Balanced accuracy	0.68	0.65	0.57
F1-score	0.71	0.71	0.60
Mathews correlation coefficient	0.40	0.12	0.12
Recall	0.68	0.98	0.82
Precision	0.75	0.55	0.43

Table 5. Results from independent geographic validation of early mortality model.

that, when permuted, produce larger degradations in performance are considered more important and receive higher importance scores.

Cancer-specific mortality
Similar to the approach used for ML model development ("Machine learning model training") and feature importance analysis presented in "Overall survival", we evaluated the feature importance to assess the contribution of each input variable to the ML model's prediction of cancer-specific mortality at early (6-month), 24-month, and 5-year time points.

Site-specific early mortality
We evaluated the significance of input variables for site-specific mortality at 6-month (early) . The result from this analysis is presented in "Model performance from external geographic validation".

Results

Patient characteristics

The 4802 patients extracted included 3121 males and 1681 females in a male-to-female ratio of 1.9:1. The mean age at diagnosis was 63.7 years (SD $\pm$ 13.0: range 12–90), interquartile range (IQR) of 18 years (73 years–55 years), and the median age 64.0 years. In terms of age categorization, 201 (4.2%) were younger (ages $\leq$ 40 years), while 4601 (95.8%) were older (>40 years). Of note, 6 (0.12%) cases between the ages 12–20 were having lip and oral cavity cancer. With respect to the HNSCC sites, the majority of the patients belong to the group having an oral cavity cancer (3143, 65.5%). A total of 433 (9.0%) had lip, 637 (13.3%) patients had oropharyngeal, 97 (2.0%) hypopharyngeal, and 492 (10.2%) had laryngeal squamous cell carcinoma. Considering tumor stage, the AJCC 7th TNM staging scheme showed that 2737 (57.0%) patients had stage T1, 1533 (11.1%) stage T2, and 532 (11.1%) had stage T3. Most of the cases (79.5%) had N0 nodal classification. Specifically, in terms of the nodal parameter, 3818 (79.5%) were N0, 855 (17.8%) were N1, and 129 (2.7%) were N3, while 4770 (98.3%) had M0 and 32 (0.7%) M1. Regarding histopathological grading, 1178 (24.5%) tumors were categorized as well-differentiated, 2483 (51.7%) as moderately differentiated, 1108 (23.1%) as poorly differentiated, and 33 (0.7%) were undifferentiated. A total of 3516 (73.2%) had HNSCC as being their first primary while 1286 (26.8%) had at least one primary prior to HNSCC diagnosis. The other clinicopathologic characteristics are briefly summarized in Table 1.

Race formed another important parameter and 4143 (86.3%) were of white origin, 210 (4.4%) black, and 449 (9.4%) were from other origins, including American Indian/AK Native, and Asian/Pacific Islander. Considering marital status, 2865 (59.7%) were married while 1937 (40.3%) were considered unmarried (single, divorced, widowed, or separated) at the time of diagnosis (Table 1). Considering the objective of this study in terms of early mortality, a total of 2989 (62.2%) patients received surgery (Sx) alone (Table 1).

The details of the treatment received at various time points are presented in Table 1. The follow-up time ranged from 0 to 155 months (mean 78.1; median 89; SD $\pm$ 46.6). The detailed description of the input variables for the remaining time points is presented in Table 1. The three time points have been presented in a single table (Table 1) to provide a quick overview on the number of cases and data variation between these three time points to facilitate better understanding and readability of our research.

Performance accuracy of the distinct ML models

For early mortality, the performance accuracy of the ML model was 70.0% and a weighted AUC of 0.77. Other performance metrics are presented in Table 2.

Feature importance analysis for overall mortality at the three different timepoints

The five topmost features identified by the ML model for early mortality were higher age at diagnosis, first primary indicator (HNSCC being the first primary), unmarried patients with T1–T3 HNSCC, T3 stage, and having hypopharyngeal or laryngeal cancers, in decreasing order of significance, were important (Fig. 4a; Supplementary 2).

For the 24-month mortality endpoint, the performance accuracy of the ML model was 86.0% and a weighted AUC of 0.72. The associated risk factors for the 24-month mortality, in decreasing order of significance were T3

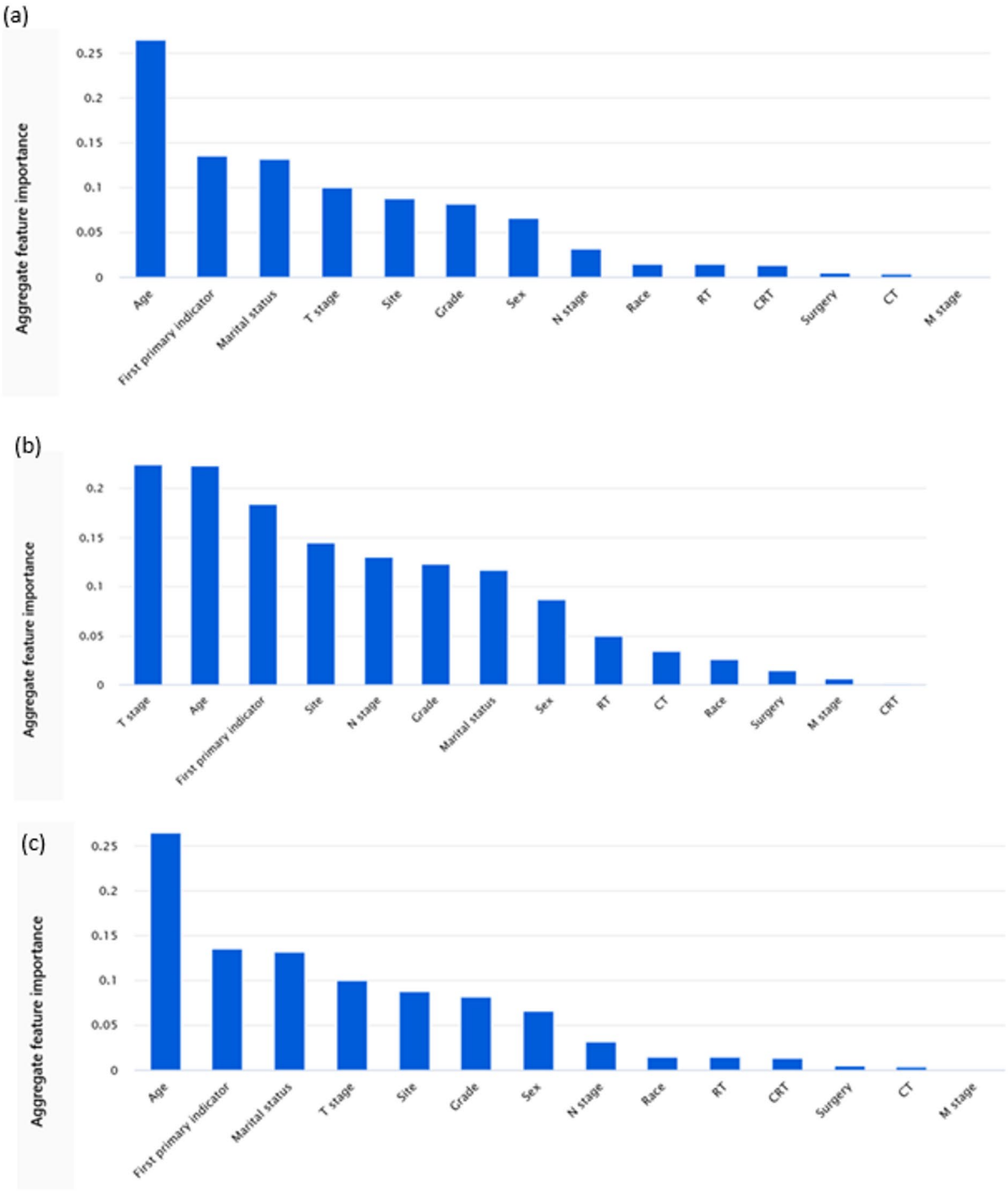

Fig. 4. (**a**) Aggregate feature importance of input variables for early mortality prediction in patients with HNSCC. (**b**) Aggregate feature importance of input variables for mortality of patients with HNSCC at 24 months. (**c**) Aggregate feature importance of input variables for 5-year mortality of patients with T1–T3 HNSCC.

stage, being elderly in terms of age at diagnosis, presence of earlier primary malignant tumors beside HNSCC, having oral cavity, hypopharyngeal, or laryngeal cancers (Fig. 4b; Supplementary 3) and N3 stage.

The associated risk factors for the 5-year mortality were found to be the same with those of early mortality with the additional inclusion of T2 stage (Fig. 4c; Supplementary 4). For 5-year mortality, the performance accuracy of the ML model was 82.0% and a weighted AUC of 0.73.

Evaluation of input features for overall mortality at the three timepoints

At all the time points examined, the age of the patients at diagnosis was always within the first two most important input features. For early mortality, we found that the risk of early mortality increases as the age increases (Fig. 5a).

As shown in Fig. 5a, the significance of early mortality appeared the same between the ages 12–55 years. Additionally, early mortality increases as the age increases from about 62 years upward. For 24-month mortality,

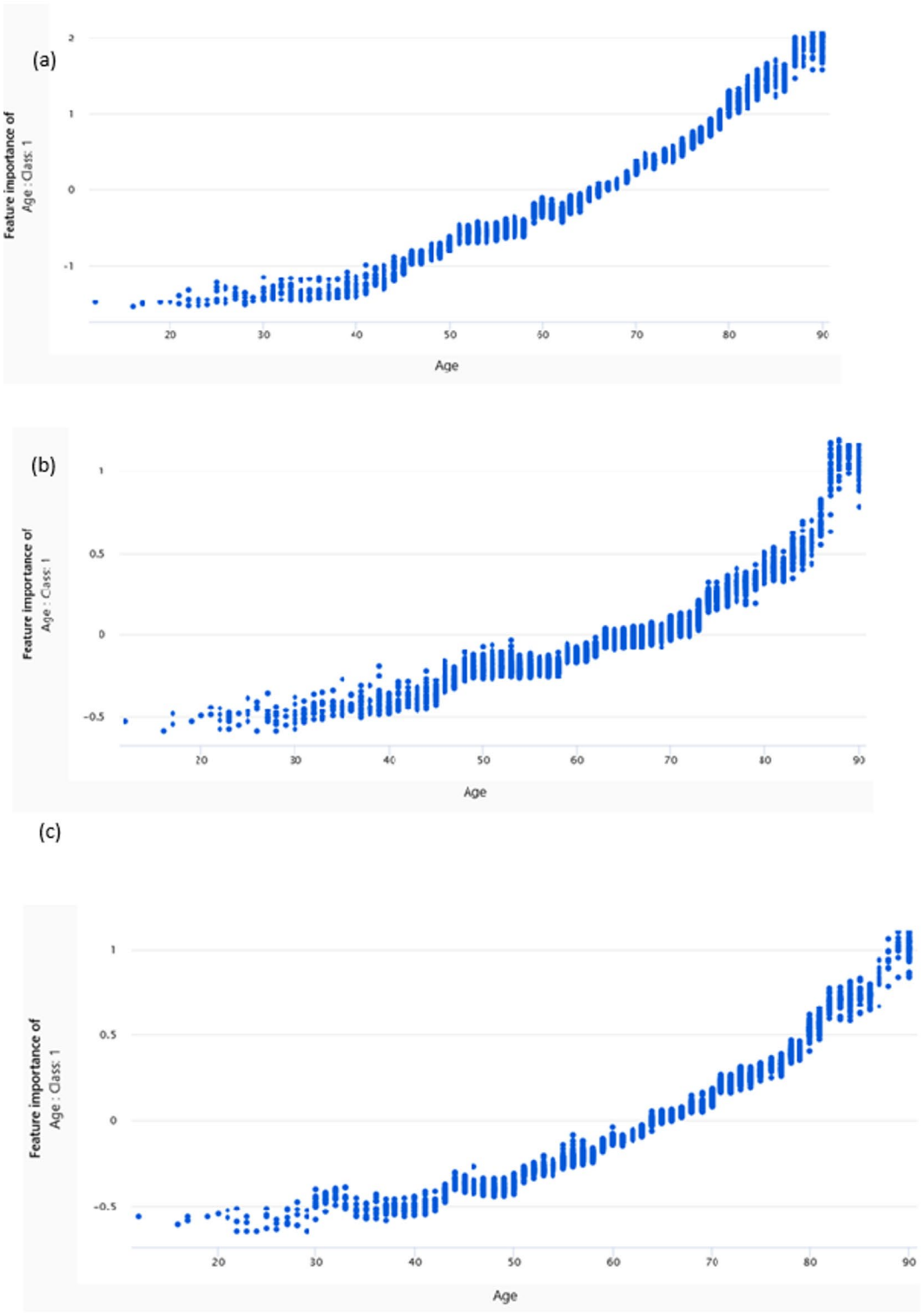

Fig. 5. (**a**) Individual feature importance for age of patients on early mortality. (**b**) Individual feature importance for age of patients on 24-month mortality. (**c**) Individual feature importance for patients age on 5-year mortality.

as the age increases, the chance of 24-month mortality increases (Fig. 5b). As shown in Fig. 5c-year mortality is more likely between ages 75 and above than between ages 60 and 75.

Ages 12–45 had the least 5-year mortality (Fig. 5c). In general, as shown in Figs. 5a–c, patients under 50 years of age, although they are few, have a low risk of death within 5 years.

Feature importance analysis for cancer-specific mortality at the three different timepoints

Our model demonstrated an accuracy of 97.8% in predicting cancer-specific early mortality. Higher T stage (T3), age at diagnosis, and grade (grade III–IV) were associated with early cancer-specific mortality at 6 months (Fig. 6a, Supplementary 5).

For the 24-month cancer-specific mortality, our model demonstrated an accuracy of 89.8%. Higher T stage (T3), tumor sites (oral cavity, hypopharynx, and larynx), and higher age at diagnosis, were associated with cancer-specific mortality at 24 months (Fig. 6b, Supplementary 6).

For the 5-year cancer-specific mortality, our model demonstrated an accuracy of 89.6%. The presence of another primary malignancy, higher age, and tumor sites (oral cavity, hypopharynx, and larynx) were associated with 5-year cancer-specific mortality (Fig. 6c, Supplementary 7).

In Table 3, we summarized the feature importance of variables in terms of cancer-specific mortality at the three different timepoints examined in our study. Similar to the result obtained for feature importance evaluation for overall mortality, the age of the patients at diagnosis was always within the first three most important input features for cancer-specific mortality. The order of significance of these variables for cancer-specific mortality is summarized in Table 3 (Fig. 6a–c, Supplementary 5–7).

The top three variable importance analysis for cancer-specific mortality at each of the time points examined in this study is summarized in Table 3.

Feature importance analysis for site-specific early mortality

For lip cancer, our model demonstrated an accuracy of 75.7% in predicting early mortality. In terms of feature importance analysis, the age at diagnosis, especially at > 50 years, higher grades (grade III–IV), and unmarried patients were associated with mortality at 6 months (Fig. 7a; Supplementary 8a–c).

Our model showed an accuracy of 96.5% in predicting early mortality in oral cancer patients. Higher age at diagnosis, higher stage (T3), and not receiving radiotherapy treatment were associated with early mortality at 6 months (Fig. 7b; Supplementary 8d–f).

Our model showed an accuracy of 81.5% in predicting early mortality in oropharyngeal cancer patients. Not receiving radiotherapy, the presence of other primaries, and being female were associated with early mortality in oropharyngeal cancer (Fig. 7c; Supplementary 8h–j).

Our model demonstrated an accuracy of 93.9% in predicting early mortality in patients with hypopharyngeal cancer. Our model found that higher stage (T3) was associated with early mortality in patients with hypopharyngeal cancer. However, there was no clear distinction between the age of patients at diagnosis and the receipt of radiotherapy since the number of patients with hypopharyngeal cancer in our data is relatively small ($n = 97$) to draw meaningful conclusions regarding the risk of 6-month mortality (Fig. 7d; Supplementary 8).

Our model showed an accuracy of 93.5% in predicting early mortality in laryngeal cancer patients. Higher age at diagnosis, T stage (T3), and not receiving radiotherapy were associated with higher risk of 6-month mortality in patients with laryngeal cancer (Fig. 7e; Supplementary 8).

Model performance from external geographic validation

The distribution of the two validation cohorts is presented in Table 4.

In terms of external geographic validation of the ML model for early mortality prediction, the predictive performance of the model is presented in Table 5. The model that was externally validated was developed without marital status and the presence of earlier primary malignant tumor besides HNSCC variables to match the external validation cohorts.

Table 5 shows how the model performed when tested independently with data outside the development environment or with data from a different geographical cohort. While the model was developed using data from the United States, the independent geographic external validation presented in Table 5 was conducted using data obtained from different geographic locations—Germany and Finland. The results showed that the model experienced a reduction in performance accuracy when externally validated (Table 5). Despite this reduction, the ML model showed a promising accuracy for predictive performance generalizability when testing such model on data outside the development environment and across distinct geographic cohorts.

Discussion

This study, to the best of our knowledge, represents the first using a machine learning (ML) technique to predict mortality at three different time points (6 months, 24 months, and 5 years) in patients with HNSCC. Additionally, this study examined and compared the most significant features that contributed to the predictive performance of this ML model for each time points. We further leveraged datasets from Germany and Finland to demonstrate independent geographic validation of the model, thereby assessing robustness, transportability, and generalizability across diverse population contexts. We conclude that the ML model could predict early mortality in HNSCC population. Similarly, it was found that higher age at diagnosis, presence of earlier primary malignant tumors beside HNSCC, unmarried patients with T1–T3 HNSCC, T3 stage, and having hypopharyngeal or laryngeal cancers, in decreasing order of significance, were important factors to be considered for early mortality in this patient population. For 24-month mortality, it was found that the associated risk factors in decreasing order of significance were T3 stage, being elderly in terms of age at diagnosis, presence of other primary tumors beside HNSCC, having oral cavity, hypopharyngeal, or laryngeal cancers, and N3 stage. The associated risk

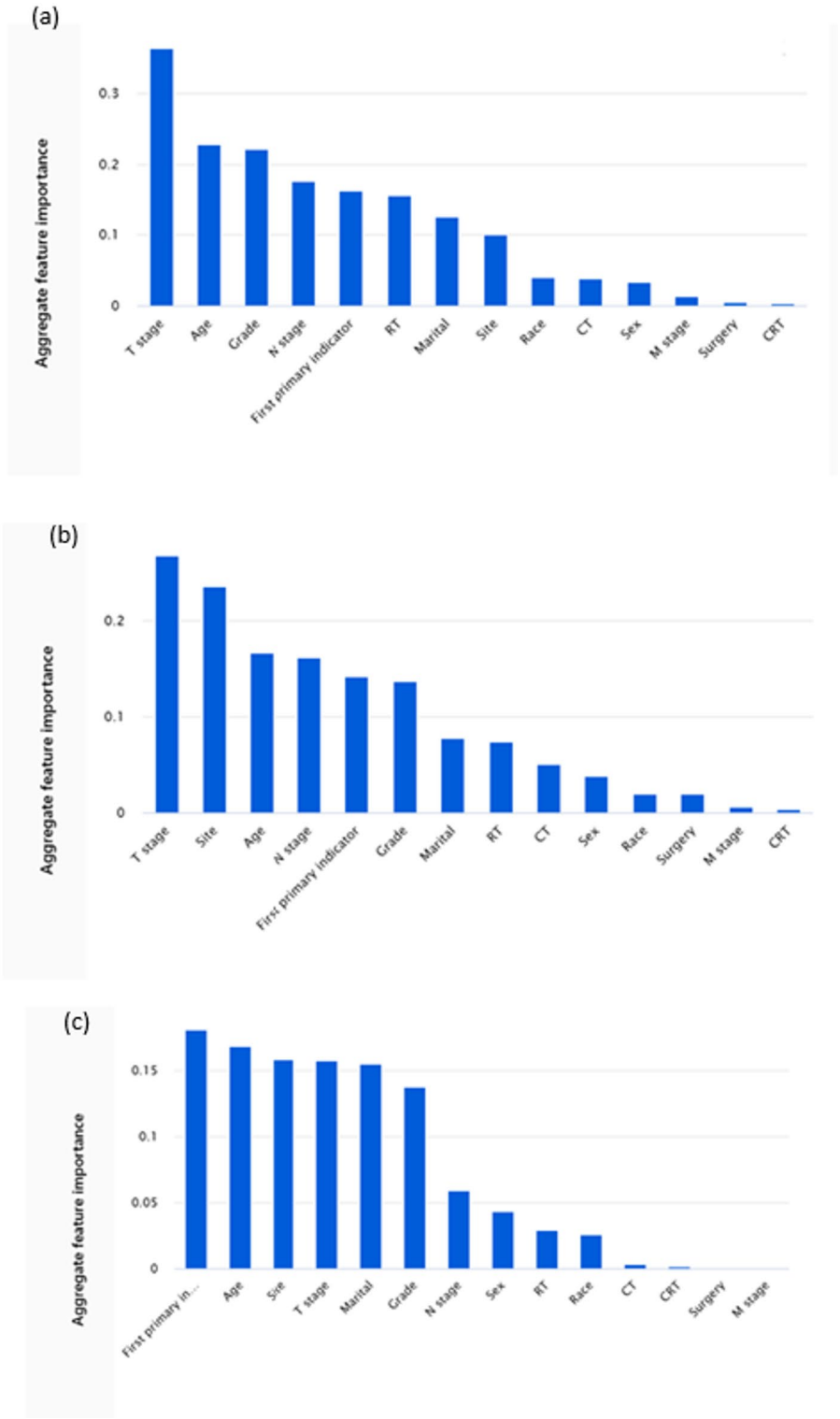

Fig. 6. (**a**) Important variables for cancer-specific mortality at 6 months. (**b**) Important variables for cancer-specific mortality at 24 months. (**c**) Important variables for cancer-specific survival at 5 years.

factors for 5-year mortality were found to be the same with those of early mortality with the additional inclusion of T2 stage. In the SEER cohort, the age of the patients emerged as the strongest predictor for early mortality. This finding is in agreement with a recent studies that highlighted that increasing age is associated with increased mortality[22,39,40].

The performance of the model, when externally validated, demonstrated its potential to predict early mortality for new patients under management consideration. Early death in the SEER database was most

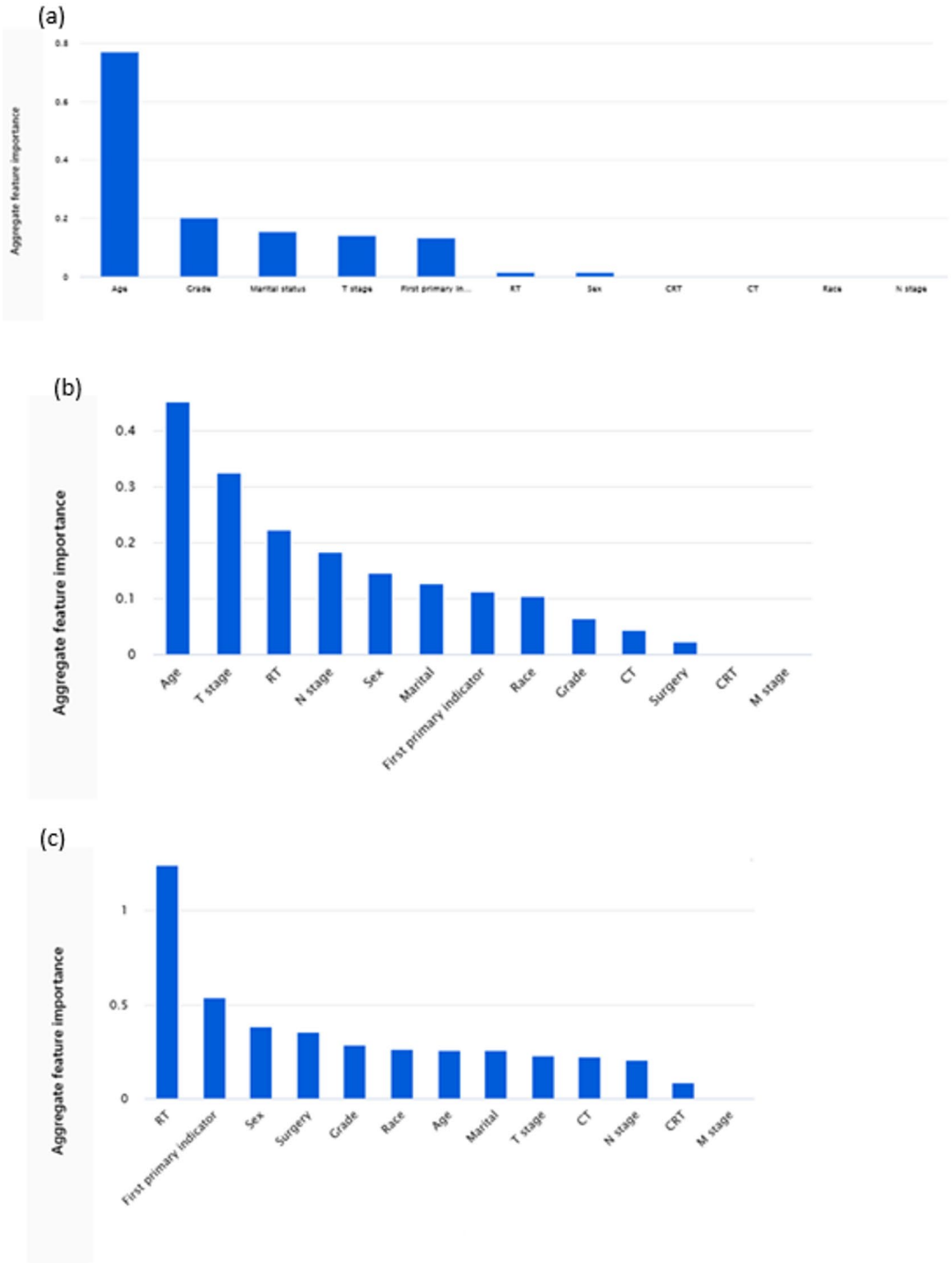

Fig. 7. (**a**) The feature importance analysis for overall survival of patients with lip cancer at 6 months. (**b**) The feature importance analysis for overall survival of patients with oral cancer at 6 months. (**c**) The feature importance analysis for the risk of 6-month mortality among patients with oropharyngeal cancer. (**d**) The feature importance analysis for mortality at 6 months of patients with hypopharyngeal cancer . (**e**) The feature importance analysis for the risk of 6-month mortality among the patients with laryngeal cancer.

common in elderly patients and also in patients with poorly or undifferentiated histological squamous cell carcinoma, unmarried, high T and N stages, and patients with hypopharyngeal and laryngeal cancers. Therefore, the treatment paradigms for HNSCC should take these findings into account regarding early mortality. The results fulfilled our goal to offer an early and timely intervention and to aid individualized and personalized treatment planning for HNSCC patients.

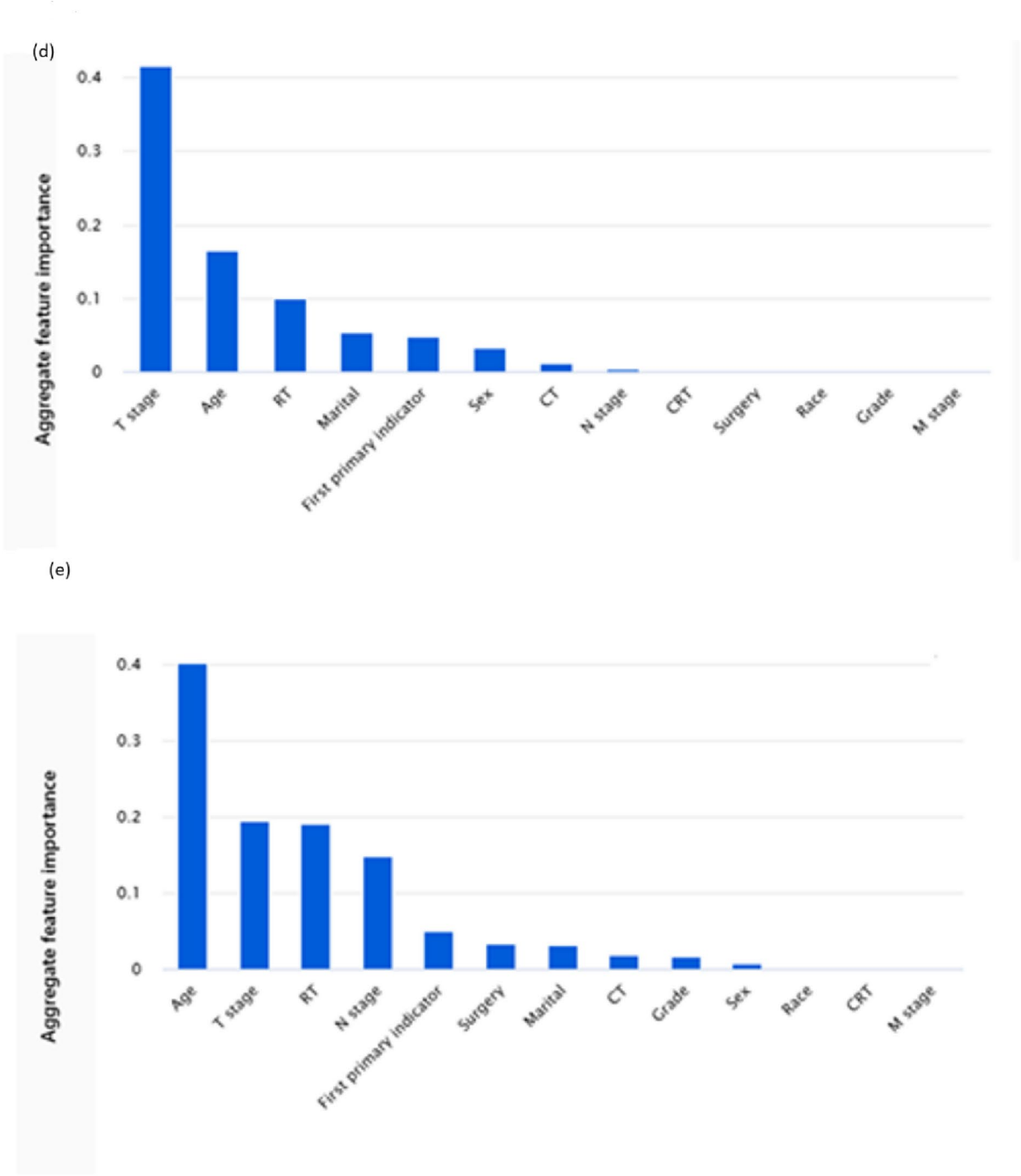

Fig. 7. (continued)

Individualized therapeutic decision-making based on early mortality prognostication remains the most difficult challenge, even for experienced clinicians. This is due to the dearth of a reliable prognostication tool for this purpose and, most importantly, due to the typical presentation of this disease at a late stage. Thus, more rapid assessments of prognosis are warranted to determine the best possible treatment recommendations[41]. In the light of potential side effects associated with treatment regimens of varying intensity in patients with HNSCC, early identification of those at risk of dying within six months may help clinicians to discuss and tailor appropriate therapeutic approaches. For example, patients with a high risk of early death may be considered for neoadjuvant and adjuvant pembrolizumab in addition to standard care, based on KEYNOTE-689, if treatment with curative intent remains the recommended alternative[42]. However, the burden and benefit of each decision need to be considered individually, as for some patients in this subgroup, this might lead to treatment-related mortality[42]. Therefore, this study leverages the ML paradigm for enhanced prediction of early mortality for patients with HNSCC. The model was developed using voting ensemble method, and this model showed

promising performance. With further validation, this model may enhance clinical decision-making in the care and management of patients with HNSCC.

In the previous work by our group, we emphasized the need for geographic validation for ML models[43]. This is necessary considering the sensitive nature of surgical, radiation, and medical oncology. It is essential that the model used for outcome prognostication in oncology is free from bias, overfitting, and it is generalizable[44]. Therefore, geographic validation of ML model is essential for determining a model's performance, generalizability, and suitability for real-world applications. Developing and using a model without proper external validation may result in using biased model[43,45]. Similarly, internal validation through hold-out or cross-validation methods may lead to biased, overly optimistic estimates of predictive performance, and often decreased generalizability to data not seen during model development[43,45–48]. Of note, temporal validation may seem like a viable solution in the absence of external validation. However, this approach still tends to yield overly optimistic performance estimates[43,45]. To avoid this, we externally validated our model using two distinct geographical cohorts to further guarantee its generalizability. Although a slight decrease in performance was observed after the external validation process, the model's performance accuracy remains promising for identifying patients at risk of early mortality. The decrease in performance may be partly explained by site variability and differences in treatment across the three cohorts. Despite this, identifying patients at risk of early mortality can guide early intervention, facilitate close monitoring, and enhance treatment planning and management.

Our model further offers insights into the most influential input features for predicting early mortality in this patient population. For example, the age of patients at diagnosis was identified as the most important feature in all the examined mortality timepoints. It appeared as one of the first two important factors in all the three examined time points. This finding is in tandem with the conclusion from earlier studies that emphasized that early mortality is a pervasive challenge with a significant impact on older adults[9,14,49–51]. This further supports our findings showing that the higher the age of patients at diagnosis, the higher the likelihood of early mortality. The effect of age on patients' early mortality was significant in older patients (~ > 65 years). This finding corresponds to the study by Bazina et al., which emphasized that the risk for early death increased in older patients[9]. Therefore, as clearly shown in all three mortality time points examined, the age of the patient at diagnosis may represent an important characteristic that should be considered[22]. Notably, in the SEER cohort used in this study, the patients under the age of 50 showed a low mortality risk at all the three time points.

We found that patients with HNSCC as the first primary malignancy are less likely to die within six months of diagnosis compared to their counterpart who have had one or more primaries before the diagnosis of HNSCC. This finding agrees with the conclusion from the study by Bertolini et al. that reported that HNSCC survivors have increased risk of developing second primary tumors which represents a major cause of morbidity and mortality in this population[52]. Remarkably, the relative risk of developing second primary in cancer survivors is higher due to persistent exposure to behavioral risk factors, genetic susceptibility, long survival after primary cancer, and the effects of therapies from the primary cancer[53,54]. As such, the diagnosis of patients who already have another primary with the onset of HNSCC may represent an indicator for early mortality. Thus, tailored surveillance and effective treatment planning are recommended to prevent early mortality.

Being married was found to be less likely to be associated with early mortality. This finding aligns with the reported conclusion from the study by Manvelian and Sbarra where it was reported that being widowed is associated with an increased risk of early mortality[55]. A similar result was found in the study by Leung et al. where strong evidence was established that being unmarried, as well as belonging to the unmarried subcategories, was negatively associated with total and cause-specific mortality[56]. The underlying assumption of the association between marital status and mortality is that being married conferred socioeconomic support and health-promoting behaviors that can contribute positively to survival[56,57]. Although the pattern of marriage differs among societies, spousal support and companionship may be pivotal during the entire HNC trajectory[60].

Furthermore, T stage was identified by our model as one of the significant determinants of early mortality in patients with HNSCC. This finding was corroborated by the studies by Guan et al. and Bazina et al., which highlighted that advanced T stage is a predictor of early death[9,51]. Furthermore, in all the three time points examined, the site of HNSCC was strongly associated with mortality. As could be expected, the mortality rates vary between these sites[22]. For example, in patients with laryngeal or hypopharyngeal cancer, nearly all deaths from the disease are expected to occur before five years have passed since diagnosis [22].

Exceptionally for 24-month mortality, as could be expected, we found N3 stage as one of important predictors patients with T1–T3 HNSCC. Considering the highly heterogeneous and aggressive malignant nature of HNSCC, high N stage represents a key indicator of disease progression and poor prognosis, directly impacting patient survival and quality of life[61]. In tandem with our finding, N stage represents a crucial independent prognostic factor affecting the treatment outcome and survival of patients with HNSCC[61–63]. Therefore, even though it remains challenging, early diagnosis of lymph node metastasis is crucial for HNSCC prognosis[10].

Our model highlighted that early mortality is associated with patients with hypopharyngeal or laryngeal squamous cell carcinoma. Though there seems to be no consensus on the best follow-up strategy for hypopharyngeal squamous cell carcinoma[64–66], this finding may further support the notion of appropriate follow-up strategy that involves every 1–3 months during the first year, every 2–6 months during the second year, and every 4–8 months during the third to fifth year[67]. This is particularly significant considering the frequency of recurrent cases in hypopharyngeal carcinoma during the first six months[68]. Therefore, all patients with hypopharyngeal carcinoma should be followed up meticulously for recurrence, especially during the first six months[68]. In recent years, no significant decrease has been observed in the mortality rate in patients with laryngeal cancer[69]. Similar to hypopharyngeal squamous cell carcinoma, advanced laryngeal carcinoma has a poor prognosis[68–70]. Additionally, its late diagnosis is directly linked to its late appearance of symptoms[71–73]. The late-stage presentation of the disease, especially where curative options are limited, may account for early death. As shown in this study, patient factors such as being elderly may lead to early mortality in laryngeal carcinoma.

Our ML model demonstrated some site-specific differences. With respect to site-specific survival, age at diagnosis, particularly ≥ 50 years, was identified as a significant predictor of early mortality in lip cancer. This finding is in tandem with other studies where most cases were prevalent in older patients, usually diagnosed between 50 and 70 years of age[74,75]. In agreement with previous studies, our model highlighted that prognosis of lip cancer is influenced by histologic grade[76–78]. Similar to lip cancer, and in alignment with previous studies, age at diagnosis was found as a significant factor for oral, hypopharyngeal, and laryngeal cancers[79–83]. Our model highlighted higher stage as an important factor for early mortality in oral cancer. This finding agrees with the conclusion from the study by Almangush et al., where it was concluded that stage forms the cornerstone in oral cancer management[84].

In tandem with the findings from the study by Hunter et al., female patients with oropharyngeal cancer were associated with worse prognosis[85]. Additionally for oropharyngeal cancer, the presence of another primary tumor (that is, oropharyngeal carcinoma not being the first primary) was associated with worse prognosis. This finding corroborates the study by Noushzady et al., where it was concluded that the presence of another primary malignancy will affect prognosis in cancer[86]. In terms of the treatment for oral cancer, patients who did not receive radiotherapy had higher early mortality. This finding is consistent with Zhu et al., who demonstrated improved survival in oral cancer patients treated with radiotherapy in addition to surgery[86]. A similar result was obtained in study by Dahlstrom et al., where patients who received radiotherapy showed better survival[87]. Similarly, our model demonstrated that patients with oropharyngeal, hypopharyngeal and laryngeal cancers who received radiotherapy had lower early mortality.

The main strength of the present work is the exploration of a ML technique to predict early mortality in patients with HNSCC s and further validating the model externally with two distinct independent cohorts. Despite this strength, our study has limitations that merit further discussion. First, the retrospective nature of the data extracted from SEER may introduce selection bias and limit the comprehensive collection of variables. This limitation is peculiar to the SEER database and retrospective studies in general. Second, there is data imbalance in the consideration for early mortality. This limitation is unexpected, as there are relatively few cases that die within six months in most cohorts[2,9], consequently increasing the likelihood of analytical bias. This should be considered in the interpretation of our results. To address this limitation, we have externally validated our model to demonstrate its generalizability. Despite this, further independent validation with a larger number of cases is warranted considering the small size of the Helsinki population used in this study. Of note, majority of the HNSCC cases included in our analysis represented lip and oral cavity. Therefore, it is important that future studies consider a more balanced data that accurately represent the frequency of different HNSCC sites to understand the factors that are significant for both early-and long-term mortality.

Furthermore, the intent of treatment (curative or palliative) for the included cases was not explicitly mentioned in the SEER database. This represents an important limitation that should be carefully considered when interpreting our results. Another limitation peculiar to the SEER database is that it lacks information about other important clinical variables (comorbidity, screening for frailty, type of chemotherapy, completeness of chemotherapy, radiotherapy techniques, IMRT/VMAT or 3DCRT), total dose, and dosimetric information. Additionally, radiation purpose (palliative or curative) has been underreported in the SEER database. Following the preprocessing of extracted data from the database, majority of the included cases were T1–T3 with the absence of N2 stage. As a result, the results presented in this study should be interpreted with caution due to these limitations. In addition, a multicenter study is warranted to further validate the results presented in this study.

In conclusion, our model showed promising performance accuracy in predicting early mortality for patients with HNSCC. The model incorporated patient demographic, clinicopathologic, and treatment parameters to estimate early mortality. This model may serve as an accurate, objective, and ancillary tool to the clinicians for enhanced decision-making[88]. Based on the results presented in this study, identifying patients at elevated risk of early death can support timely, individualized therapeutic decision-making, and potentially avoid unwarranted aggressive treatments and improving survival outcomes. Due to the number of occurrences of early mortality (low percentage) that is typically present in HNSCC cohorts, multi-institutional collaboration is warranted to develop a viable model. Thus, large-scale external validation is important. In addition, data set including information on cancer extension and resection margins in surgical cases, information on treatment intent, extra-nodal extension, and human papilloma virus (HPV) status should be considered in future research to identify risk factors associated with early death.

Data availability

The datasets generated in this study are available from the corresponding author upon reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

Informed consent for the data used in this study
The Ethics Committee of the Jena University Hospital approved the study (IRB No. 3204-07/11) with a waived requirement for informed consent since the study had a non-interventional retrospective design and all data were analysed anonymously. For Helsinki data, the study permission was granted by the Research Administration of the Helsinki and Uusimaa Hospital District (HUS/307/2019). The SEER data is a public data with informed consent obtained for all the patients as stated by the National Health Institute (NIH). The ethical permission to use SEER data was granted to the first author.

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