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OShnscc: a novel user-friendly online survival analysis tool for head and neck squamous cell carcinoma based on RNA expression profiles and long-term survival information

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Head and neck squamous cell carcinoma (HNSCC), as the most common type (>90%) of head and neck cancer, includes various epithelial malignancies that arise in the nasal cavity, oral cavity, pharynx, and larynx. In 2020, approximately 878 000 new cases and 444 000 deaths linked to HNSCC occurred worldwide (Sung et al., 2021). Due to the associated frequent recurrence and metastasis, HNSCC patients have poor prognosis with a five-year survival rate of 40%–50% (Jou and Hess, 2017). Therefore, novel prognostic biomarkers need to be developed to identify high-risk HNSCC patients and improve their disease outcomes.

The expression of certain genes, especially oncogenes, has been reported to exhibit significant relationships with cancer prognosis, such as genes epidermal growth factor receptor (*EGFR*) and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) that have prognostic value in HNSCC (Polanska et al., 2014). However, thus far, few reported biomarkers have been applied in clinical management because these were usually identified in a small number of patients and lacked independent validation (Kim et al., 2014; Fauzi et al., 2020). With the availability of gene expression profiles and related clinical follow-up information in public databases, such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO), the expression profiles of large cohorts could be used for the identification and evaluation of prognostic biomarkers. However, special bioinformatics techniques are needed to analyze and integrate these complex multidimensional omics and clinicopathological data, which has been hindering most researchers without much bioinformatics skills. The application of such bioinformatics tools has shown success in basic and translational medicine studies, especially in the field of biomarker development (Zhang et al., 2019). Unfortunately, a suitable and easy-to-use bioinformatics tool to allow the fast screening and evaluation of prognostic biomarkers in different HNSCC cohorts is still lacking.

Therefore, in the current study, we developed the Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma (OShnscc), which could offer a new possibility for clinicians and researchers to assess the prognostic value of genes independently in multiple HNSCC cohorts. The development process of OShnscc is presented in Fig. 1. This web-based tool can be accessed at http://bioinfo.henu.edu.cn/HNSC/HNSCList.jsp.

OShnscc contains a total of 1366 clinical cases from nine datasets, including one TCGA dataset and eight GEO datasets. In this tool, six types of survival terms are provided for survival analysis, including

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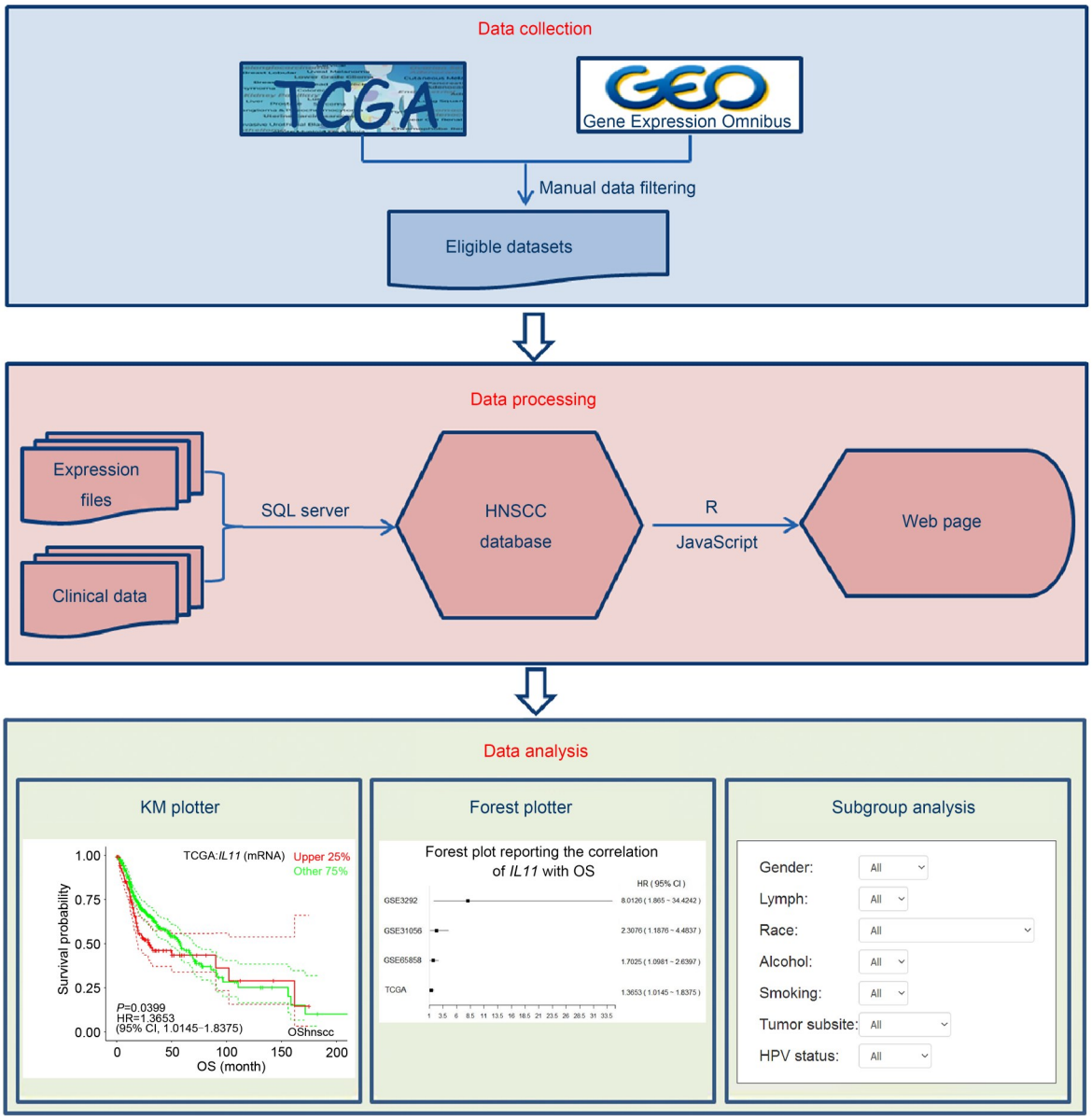


Fig. 1 Architecture diagram of the development process of OShnscc. OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; TCGA: The Cancer Genome Atlas; HNSCC: head and neck squamous cell carcinoma; KM: Kaplan-Meier.

overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), progression-free survival (PFS), disease-free interval (DFI), and progression-free interval (PFI). The survival terms have been described in detail in original studies (Wichmann et al., 2015; Liu et al., 2018). In brief, OS is estimated from the time of diagnosis to the last follow-up, and DSS is similar to OS but only includes patients who died of cancer. DFS is measured from the time of primary recovery to the first observation of relapse or death from any cause by the last follow-up, and DFI is similar to DFS but excludes patients in Stage IV or those who deceased without relapse. PFS is defined from the registration date until the date of detection of definitive disease progression, recurrence, metastasis, new primary tumors in all sites, or death from any cause, and PFI is similar to PFS but excludes patients who died from causes other than cancer. A total of 888 (65%) patients are male, and the median age is 59 years; 731 (54%) patients have OS information, and the median OS time is 24 months.

Patients without either clinical follow-up time or gene expression data were removed. The patient clinical characteristics, including tumor node metastasis (TNM) stage, grade, gender, smoking history, lymph invasion, human papilloma virus (HPV) status, and race, were also included and set as confounding clinical factors for subgroup analysis in OShnscc. The clinical characteristics and the detailed items of all datasets in OShnscc are summarized in Tables 1 and S1, respectively.

Six clinical characteristics including TNM stage, grade, age, gender, race, and tumor subsite were measured for association with the OS of HNSCC patients in the OShnscc datasets. As shown in Fig. 2, the clinical factors including TNM stage (Fig. 2a), grade (Fig. 2b), age (Fig. 2c), gender (Fig. 2d), race (Fig. 2e), and tumor subsite (Fig. 2f) showed significant associations with the OS of HNSCC patients (P<0.0001, P=0.0365, P=0.0007, P=0.0255, P=0.0273, and P=0.0091, respectively), which was consistent with previous reports (Pai and Westra, 2009; Polanska et al., 2014; Naghavi et al., 2016).

The main function of OShnscc is to evaluate and verify the prognostic value of a given gene in HNSCC. On its home page, OShnscc provides a fast survival analysis model using the default parameter of "Data Source" as "All," the "Survival" term as "OS," and "Split patients by" cutoff as "Upper 25%." The user only needs to input the genes of interest in the term "Gene symbol" and click the "Survival analysis" button. Then, a forest plot and a table that summarize the prognostic values, including hazard ratio (HR) with 95% confidence interval (CI) and the log-rank P value of queried genes in each dataset of OShnscc, will be generated. Taking the transmembrane p24 trafficking protein 4 (*TMED4*) gene as an example, if the user inputs the gene symbol "*TMED4*" and then clicks the "Survival analysis" button, a forest plot and a table containing the prognostic value of *TMED4* will be presented on the output webpage. The results shown in Fig. 3 indicate that the high expression of *TMED4* is associated with the poor OS of HNSCC patients in the dataset of TCGA (n=499, P<0.0001, HR=1.9695, 95% CI=1.4794–2.6220) and GSE3292 (n=33, P=0.0150, HR=5.9593, 95% CI=1.4137–25.1212), while no significant relationship was found between *TMED4* expression and the OS of HNSCC patients in the dataset of GSE31056 (n=96, P=0.3351, HR=0.6661, 95% CI=0.2916–1.5218) or GSE65858 (n=270, P=0.4196, HR=1.2043, 95% CI=0.7668–1.8913). When the user query of a gene with a reported prognostic role is submitted, a reminder stating "The query gene has been previously reported as a prognostic biomarker in [Reference]" will be presented underneath the analysis result on the output page. By clicking on the "Go" button on the

Table 1 Clinical characteristics of HNSCC datasets used in OShnscc

Data source	Platform	Sample size	No. of deaths	Median age (years)	Median OS (months)	Male (%)	HPV status (+/−/NA)	Stage I/II/III/IV/NA (%)	Smoking (%)	Tumor subsite	Survival term
TCGA	Illumina HiSeqV2	523	220	61	21.50	73.04	35/239/249	5.16/13.96/15.68/51.05/14.15	75.14	OC, OP, HP, L, T	OS, DSS, PFS, DFI, PFI
GSE10300	GPL570	44	16	53		79.55		2.27/6.82/18.18/43.18/29.55	65.91	OC, OP, HP, L	RFS
GSE27020	GPL96	109		64		95.45		11.01/16.51/33.03/39.45/0	99.08	L	DFS
GSE25727	GPL8432	56		60		92.86			87.50	L	DFS
GSE31056	GPL10526	96	36	59	13.54	62.50		0/20.83/3.13/37.50/38.54		OC	OS, DFS
GSE3292	GPL570	33	8	56	24.00	81.82		6.06/6.06/24.24/57.58/6.06		OC, OP, HP, L	OS, DFS
GSE39366	GPL9053	138	68	57		68.84	14/82/42	5.80/10.14/20.29/60.87/2.90	78.26	OC, OP, HP, L	RFS
GSE41613	GPL570	97	51		26.30	68.04	0/97/0			OC	OS, DSS
GSE65858	GPL10588	270	94	59	27.90	82.59	73/196/1	6.67/13.70/13.70/65.93/0	88.52	OC, OP, HP, L	OS, PFS
Total		1366	493								

HNSCC: head and neck squamous cell carcinoma; OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; OS: overall survival; HPV: human papilloma virus; NA: not available; TCGA: The Cancer Genome Atlas; OC: oral cavity; OP: oropharynx; HP: hypopharynx; L: larynx; T: tonsil; DSS: disease-specific survival; PFS: progression-free survival; DFI: disease-free interval; PFI: progression-free interval; RFS: relapse-free survival; DFS: disease-free survival. PFS, DFI, and PFI were defined by Wichmann et al. (2015) and Liu et al. (2018).

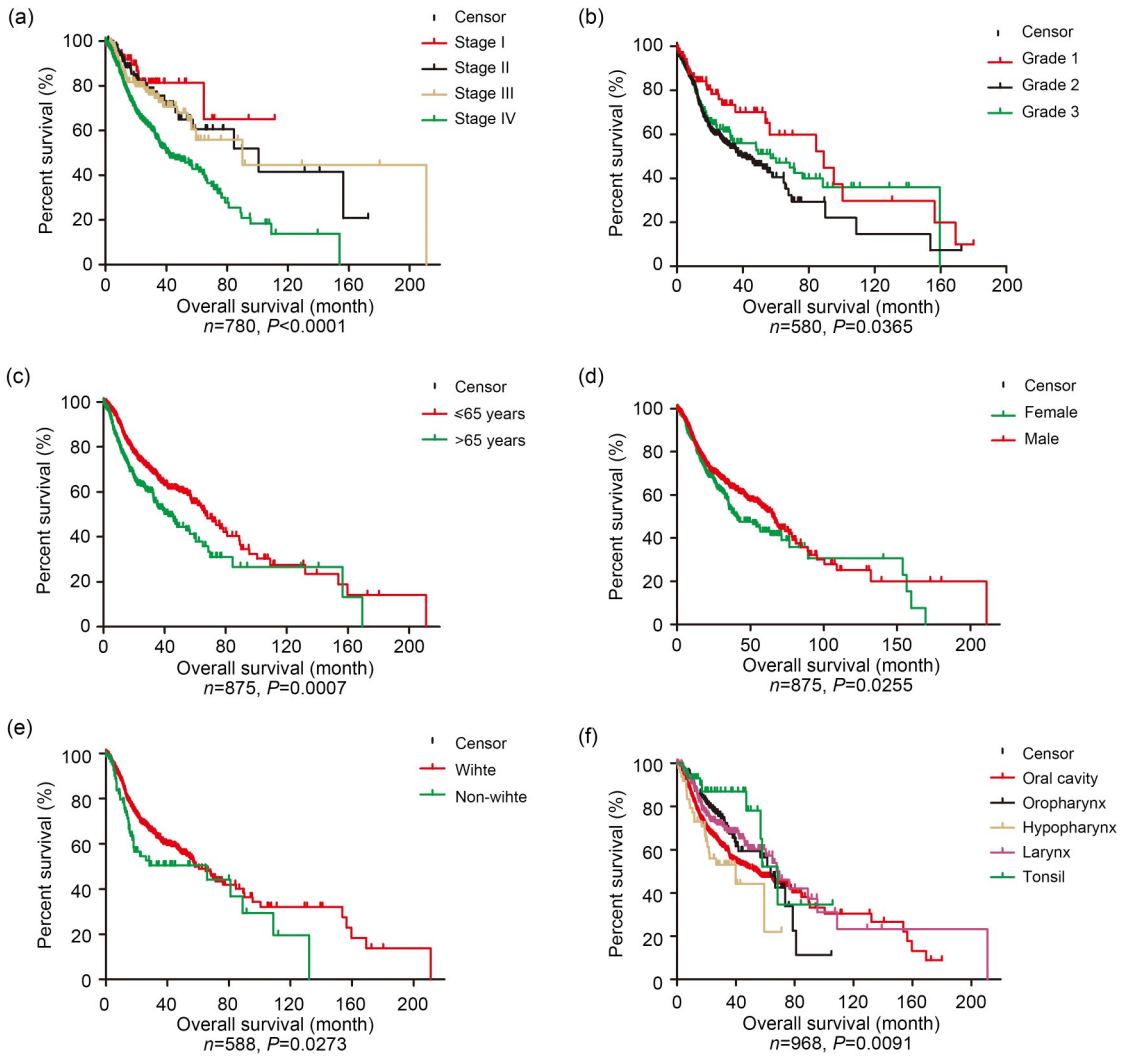
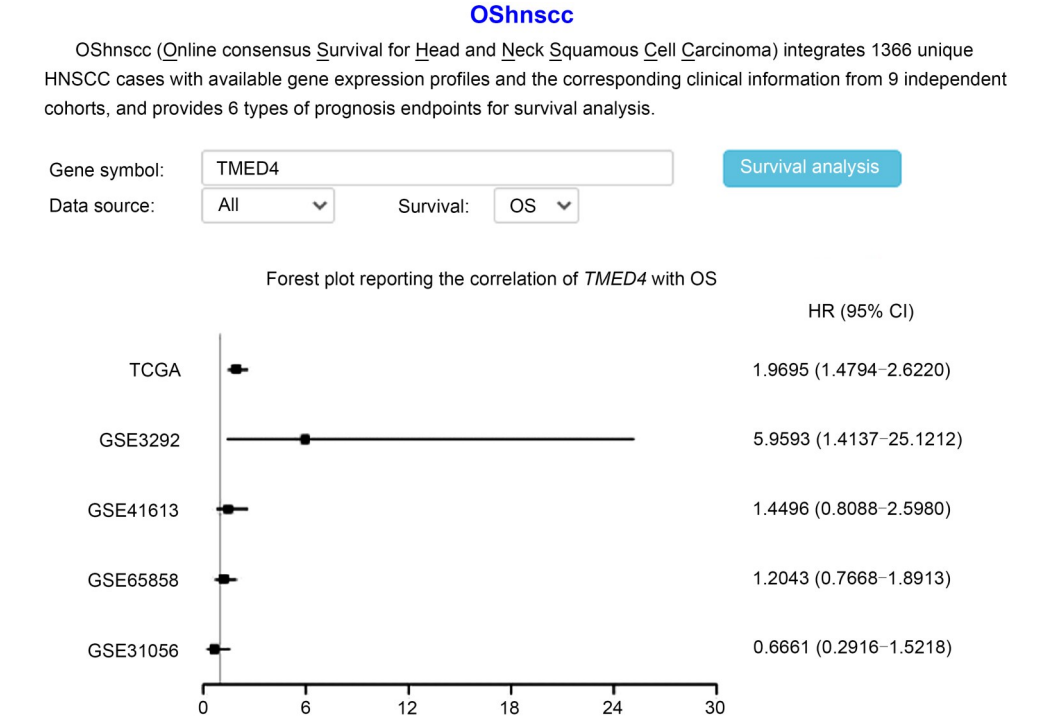


Fig. 2 Survival analysis by clinical factors for all datasets in OShnscc. (a) TNM stage; (b) Grade; (c) Age; (d) Gender; (e) Race; (f) Tumor subsite. OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; TNM: tumor node metastasis.

right side of the table, the user can easily acquire the Kaplan-Meier (KM) plots of *TMED4* for individual cohorts such as the TCGA dataset (Fig. 4).

The OShnscc platform also provides diverse options of parameters for survival analysis. Through choosing the datasets in the term "Data source," OShnscc turns to the individual dataset page, and several parameters with 2–5 options are provided. For example, users may want to evaluate the association between the gene of interest and the disease prognosis of patients from the TCGA dataset, and subsequently choose the TCGA dataset in "Data source." Two main parameters including "Survival" and "Split patients by" and nine optional parameters including TNM stage, grade, gender, etc. are displayed on the TCGA webpage (Fig. 5). Users only need to type the gene symbol, select the prognostic endpoint in "Survival" and the cutoff value in "Split patients by," and then click the "Kaplan-Meier plot" button for the survival curve with HR, 95% CI, and log-rank *P* value to be graphically displayed on the webpage. In addition, optional parameters including TNM stage, HPV status, smoking history, gender, lymph, histological type, and race are also provided for subgroup analysis to limit the prognosis in a subgroup for the intended clinical factor of HNSCCs.

In order to measure the performance of OShnscc and the repeatability of prognostic biomarkers reported in the literature, a total of 39 prognostic genes reported by 36 studies were collected for testing in OShnscc. As shown in Tables S2 and S3, 38 out of 39 previously



Univariate Cox regression analysis of *TMED4* expression with OS in each dataset of OShnscc

Dataset	*P* value	HR	95% CI	Prognostic	
TCGA	<0.0001	1.9695	1.4794–2.6220	Poor	Go
GSE3292	0.0150	5.9593	1.4137–25.1212	Poor	Go
GSE41613	0.2123	1.4496	0.8088–2.5980		Go
GSE31056	0.3351	0.6661	0.2916–1.5218		Go
GSE65858	0.4196	1.2043	0.7668–1.8913		Go

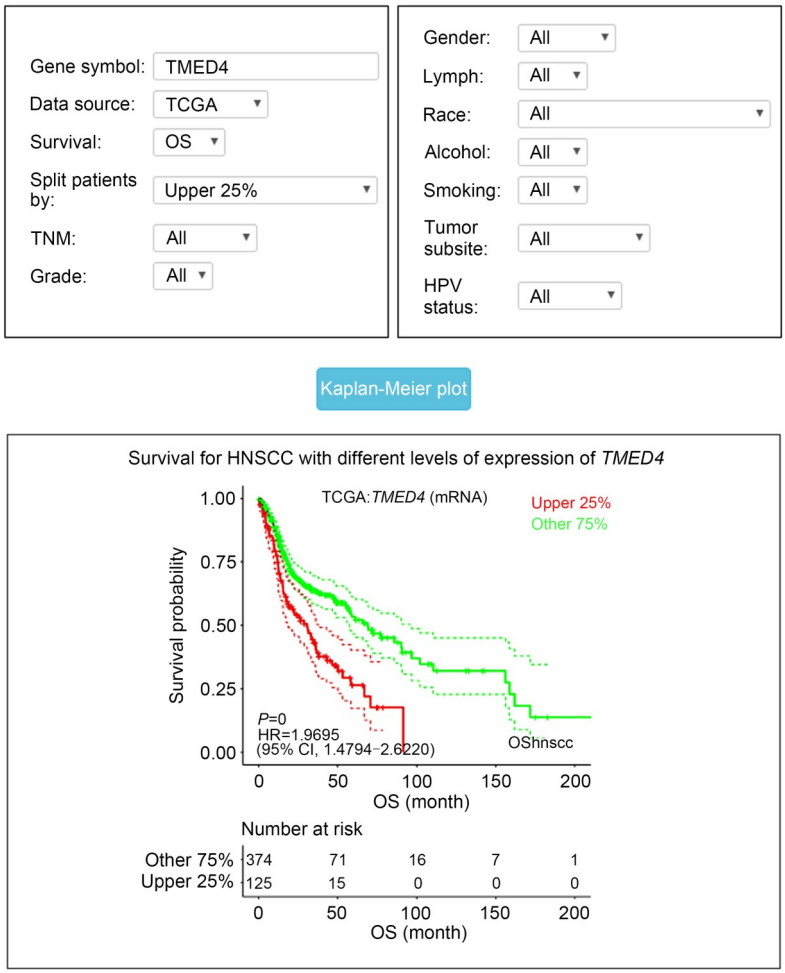
Note: cutoff: upper 25% vs. other 75%.

Click here to see the definitions of survivial terms including overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), progression-free survival (PFS), disease-free interval (DFI), and progression-free interval (PFI).

Fig. 3 Summary of prognostic analysis of *TMED4* expression in OShnscc using default parameters. *TMED4*: transmembrane p24 trafficking protein 4 gene; OS: overall survival; TCGA: The Cancer Genome Atlas; HR: hazard ratio; CI: confidence interval.

reported genes (97%) have been confirmed for their prognostic values in OShnscc, and 16 out of 39 genes (41%) showed significant association with HNSCC outcomes for at least two independent datasets in OShnscc. However, one gene (SRY-box transcription factor 4 (*SOX4*)) did not show any significance for prognosis in any cohort from OShnscc. A total of 39 previously reported prognostic genes, except *SOX4*, were confirmed in at least one of the HNSCC cohorts in OShnscc. The discrepancy of the prognostic performance of *SOX4* between OShnscc and the literature is likely due to race (Naghavi et al., 2016). The race of cohorts reported in the literature was Asian (Korea), while the cohort included in OShnscc is mostly the Caucasian population. The survival analysis of previously reported prognostic biomarkers in OShnscc demonstrated that OShnscc performs well in evaluating the prognosis of genes and can be a highly useful tool for screening and evaluating prognostic biomarkers for HNSCC patients.

OShnscc can be used to facilitate discovering new prognostic biomarkers. Through OShnscc, we found that interleukin 11 (*IL11*) has a significant association with the OS of HNSCC patients in five OShnscc datasets (Figs. 6a–6e). Highly expressed *IL11* is significantly associated with poor OS in the HNSCC datasets including TCGA (n=499, P=0.040, HR=1.365, 95% CI=1.015–1.838), GSE31056 (n=96, P=0.007, HR=2.475,



DFI and PFI were defined by Liu et al. [Liu, J., Lichtenberg, T., Hoadley, K. A. et al. (2018). An integrated TCGA pan-cancer clinical data resource to drive high-quality survival outcome analytics. Cell,173(2), 400-416.]

Fig. 4 Kaplan-Meier curve based on *TMED4* expression in OShnscc using default parameters of "TCGA" as data source, "OS" for survival, and "Upper 25%" for patients splitting. *TMED4*: transmembrane p24 trafficking protein 4 gene; OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; TCGA: The Cancer Genome Atlas; HNSCC: head and neck squamous cell carcinoma; TNM: tumor node metastasis; mRNA: messenger RNA; HR: hazard ratio; CI: confidence interval; OS: overall survival; HPV: human papilloma virus; DFI: disease-free interval; PFI: progression-free interval.

95% CI=1.280–4.785), GSE3292 (n=33, P=0.005, HR=8.013, 95% CI=1.865–34.424), GSE65858 (n=270, P=0.017, HR=1.703, 95% CI=1.098–2.640), and GSE41613 (n=97, P=0.047, HR=1.838, 95% CI=1.010–3.347). Moreover, HNSCC patients with high *IL11* expression levels had shorter OS (n=995, HR=1.64, 95% CI=1.32–2.03) based on the results of meta-analysis (Fig. 6f). To our knowledge, *IL11* is a member of glycoprotein-130 (GP-130) cytokines, and over-expressed *IL11* has been reported in tumorigenesis through the Janus kinase (JAK)-signal transducers and activators of transcription 3 (STAT3) pathway in cancers, including breast cancer, colorectal cancer, and gastric cancer (Xu et al., 2016). In addition, the upregulation of *IL11* has been shown to be associated with shortened survival in clear cell renal cell carcinoma (Pan et al., 2015), non-small cell lung cancer (Zhao et al., 2018), and breast cancer (Hanavadi et al., 2006). This gene has not been previously reported as a prognostic biomarker in HNSCC, and thus it should be validated in a clinical study for novel prognostic biomarker development. Based on the above data, we hypothesize that *IL11* could be a potential candidate for further experimental verification.

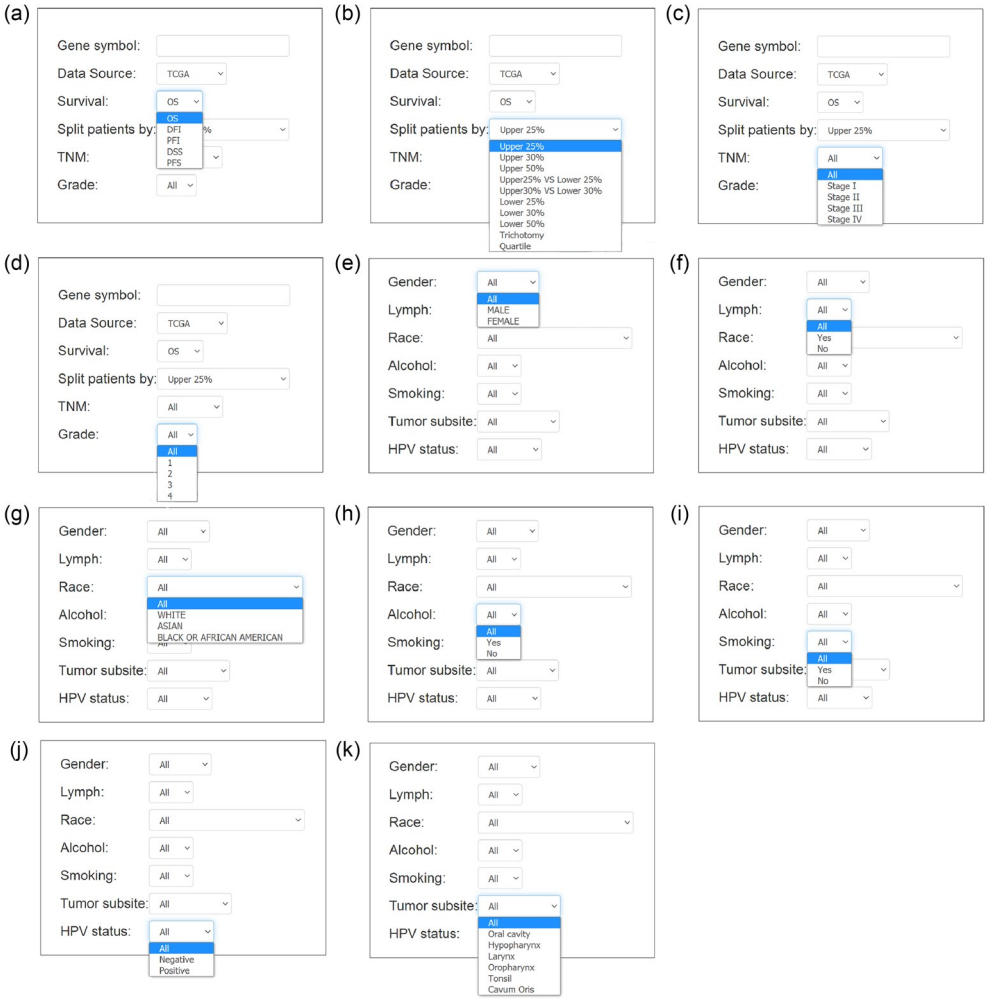


Fig. 5 Options of main input parameters and clinical factors provided in OShnscc. (a) Survival term; (b) Split patients by; (c) TNM stage; (d) Grade; (e) Gender; (f) Lymph invasion; (g) Race; (h) Alcohol; (i) Smoking; (j) Tumor subsite; (k) HPV status. OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; TNM: tumor node metastasis; HPV: human papilloma virus.

Currently, several messenger RNA (mRNA)-focused survival analysis tools exist, such as Gene Expression Profiling Interactive Analysis (GEPIA) (Tang et al., 2017), KM plotter (Nagy et al., 2018), and UALCAN (Xu et al., 2021). Nevertheless, most of these tools are mainly or exclusively based on datasets collected from the TCGA database, have limited number of HNSCC cases, and lack individual cohorts for independent validation. In comparison to these tools, OShnscc has several unique features: (1) it is an online survival assessment tool specifically for HNSCC, and contains by far the largest number of HNSCC cases (1366 cases) for prognostic analysis; (2) it enables users to evaluate the prognostic value of the queried gene independently in individual cohorts, which could generate more robust results for prognostic analysis; (3) it allows users to perform survival analysis for subgroups by filtering HNSCC patients through the use of different terms of clinical confounding factors. However, OShnscc has limitations in survival analysis. For example, although it features the largest number of HNSCC patients, the corresponding case numbers for the prognostic analysis of recurrence and metastasis are still low. Nevertheless, we aim to expand the number of HNSCC cases for OShnscc once the novel relative HNSCC datasets become available.

In summary, OShnscc is proposed as a publicly available, free online web tool for the rapid analysis of the prognostic values of genes in HNSCC. This

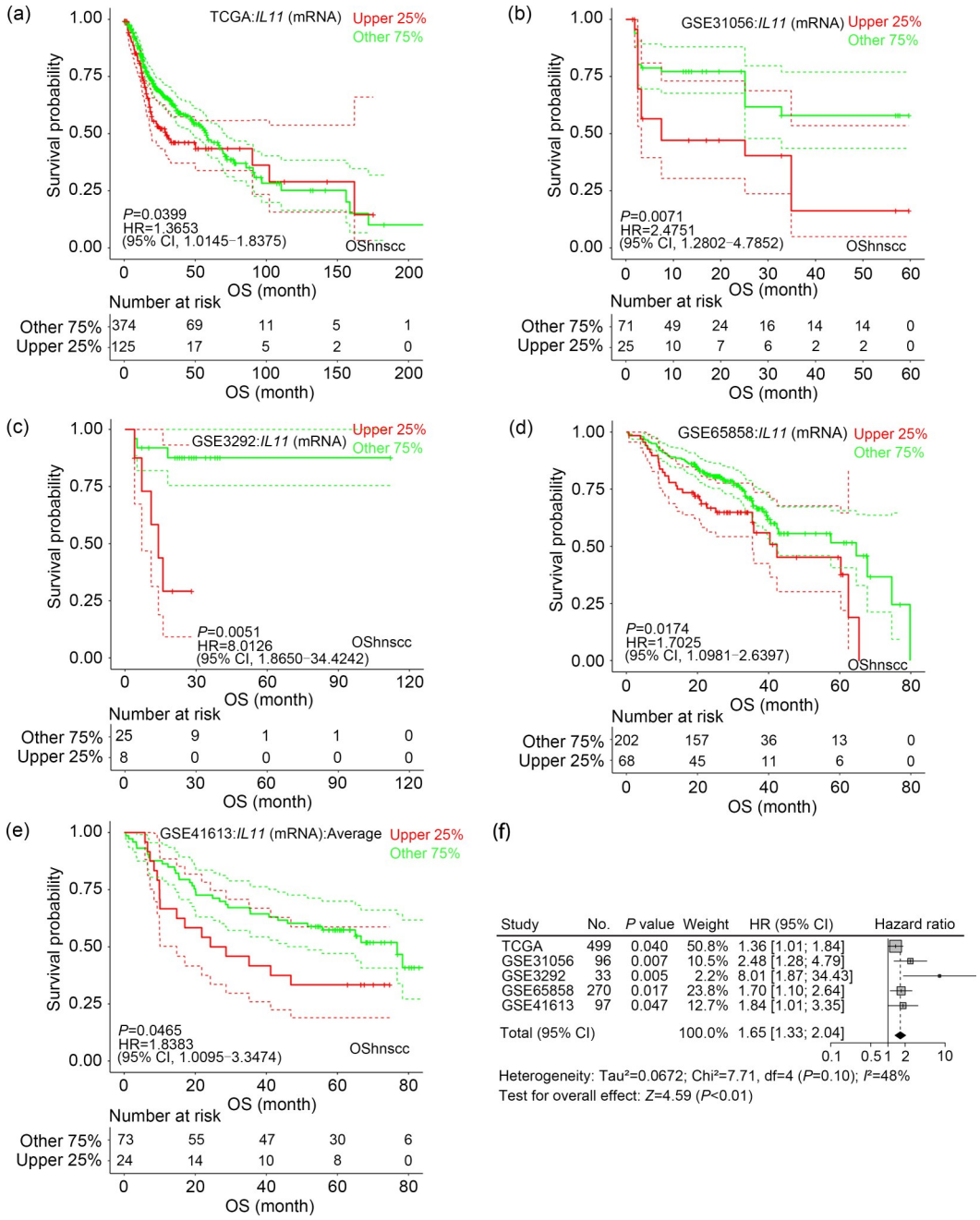


Fig. 6 Survival analysis of *IL11* gene in OShnscc. (a–e) Kaplan-Meier survival curves of *IL11* with OS in the data source of TCGA (a), GSE31056 (b), GSE3292 (c), GSE65858 (d), GSE41613 (e); (f) Forest plots for the meta-analysis of the prognostic values of *IL11* gene for OS analysis in OShnscc. *IL11*: interleukin 11; OShnscc: Online consensus Survival tool for Head and Neck Squamous Cell Carcinoma; TCGA: The Cancer Genome Atlas; OS: overall survival; HR: hazard ratio; CI: confidence interval; mRNA: messenger RNA.

tool is user-friendly, allowing researchers with limited bioinformatics background to screen and evaluate the prognostic values of genes for different cohorts of HNSCC, which may accelerate the clinical development of prognostic biomarkers in HNSCC. Upon the release of additional HNSCC datasets, we will keep updating the database of OShnscc to perform prognostic analysis for HNSCC patients at a large scale.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

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Author contributions

Guosen ZHANG performed data collection, developed the web tool, and wrote and edited the manuscript. Qiang WANG and Xinlei QI performed data collection and developed the web tool. Huimin YANG, Xiaodong SU, Manman YANG, Chao JIANG, and Yang AN contributed to data collection and analysis. Hong ZHENG, Lu ZHANG, and Wan ZHU performed data analysis and paper writing. Jiancheng GUO and Xiangqian GUO contributed to the study design, data analysis, writing and editing of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Guosen ZHANG, Qiang WANG, Xinlei QI, Huimin YANG, Xiaodong SU, Manman YANG, Chao JIANG, Yang AN, Hong ZHENG, Lu ZHANG, Wan ZHU, Jiancheng GUO, and Xiangqian GUO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information

Fig. S1; Tables S1–S3; Materials and methods