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An Inflammation-Immunity Classifier of 11 Chemokines for Prediction of Overall Survival in Head and Neck Squamous Cell Carcinoma

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Background: Chemokines are important in inflammation, immunity, tumor progression, and metastasis. The purpose of this research was to find an integrated-RNA signature of chemokine family genes to predict the survival prognosis in head and neck squamous carcinoma (HNSC) patients.

Material/Methods: Relevant data of 504 HNSC patients were extracted from The Cancer Genome Atlas (TCGA) database. Through analyzing RNA sequencing data, the univariate Cox model was used to identify chemokine family genes associated with survival and then to develop a multiple-RNA signature in the training set. The prediction value of this multiple-RNA signature was further verified in the validation and entire sets. The receiver operating characteristic curves were used to assess the predictive value of this multiple-RNA signature.

Results: Eleven chemokines were included in this prognostic signature. Based on this 11-chemokine signature, we further categorized patients as high or low risk. Compared with low-risk patients, high-risk patients had shorter overall survival (OS) time in the training set [hazard ratio (HR)=3.497, 95% confidence interval (CI)=2.142–5.711, p<0.001], validation set (HR=3.575, 95% CI=1.988–6.390, p<0.001), and entire set (HR=3.416, 95% CI=2.363–4.939, p<0.001). This 11-chemokine signature was an independent prognostic factor for OS in these datasets (p<0.05). The AUC values for predicting overall survival within 48 months in the training, validation, and entire sets were 0.71, 0.69, and 0.69, respectively.

Conclusions: This 11-chemokine signature could serve as a reliable prognostic tool for HNSC patients and might be useful to guide individualized treatment or even gene target therapy for high-risk patients.

MeSH Keywords: Chemokines, CC • Head and Neck Neoplasms • Survival Analysis • Transcriptome

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Background

Head and neck squamous cell carcinoma (HNSC) is the sixth most common and frequently lethal cancer worldwide, with about 350 000 cancer-related deaths per year [1]. The current staging system has limitation in identifying high-risk HNSC because large variability in clinical outcomes was found in same-stage patients [2–6]. To identify high-risk HNSC patients, new prognostic biomarkers are urgently needed for guiding the personalized treatment.

Chemokines are a particular group of cytokines that were originally described as being chemotactic to leukocytes [7]. They can bind to 7-transmembrane domain G-protein-coupled receptors that are predominantly expressed by leukocytes [8]. Chemokines are classified into 4 different subgroups (CXC, CC, CX3C, or C) depending on the position of the conserved cysteine residue [9]. Chemokines are closely associated with inflammation, immunity, tumor development, and prognosis [10–12]. Chemokines play vital roles in all phases of oncogenesis, tumor growth, angiogenesis, malignant transformation, and metastatic dissemination in HNSC patients [9–13]. Many studies have shown that these single biomarkers cannot be widely used for the prediction of tumor prognosis because of their controversial conclusions and the heterogeneity between tumors [14–17]. Risk stratification may require combined multiple-molecular biomarkers. The gene expression profiles were produced simultaneously by high-throughput sequencing during the past 2 decades. Therefore, we can use a bioinformatic discovery approach to identify a multiple-RNA classifier that can improve the prediction of overall survival in HNSC patients.

Material and Methods

Data collection

The clinical data for age, gender, primary sites, and clinical stage were downloaded from the TCGA database using the cBioPortal platform (2018.12.01). The inclusion criteria were: (i) histological diagnosis of HNSC; and (ii) adequate clinical characteristics (gender, age, primary sites, clinical stage, overall survival status, and time). Altogether, 504 HNSC patients were included and randomly divided into the training set (n=252) and validation set (n=252, detail shown in Table 1). The numbers of stage I, II, III, and IV patients were 20, 97, 104, and 283, respectively. In addition, 10 HNSC patients had received neoadjuvant chemoradiotherapy; the other 494 patients had not. There were 334 HNSC patients <65 years, and the other 170 patients were >65 years. A total of 371 patients were male, and the other 133 patients were female. The RNA expression data of level 3 were downloaded from the cBioPortal platform and normalized. Chemokines were selected for which the expression data of >80% of HNSC patients were more than 0.

Statistical analysis

In the training set (n=252), we estimated the expression of the selected chemokines with overall survival (OS) by using the univariate Cox model. The candidate chemokines with a p-value of less than 0.05 were used to construct a predictive model by a multivariate Cox model. We calculated the prognostic risk score by the selected chemokines and their regression coefficients in the multivariate Cox model [18–20], as follow: Risk Score=expCCL2 * βCCL2+expCCL7 * βCCL7+expCCL22 * βCCL22+expXCL2 * βXCL2+expCXCL5 * βCXCL5+expCXCL8 * βCXCL8+expCCR4 * βCCR4+expCCR6 * βCCR6+expCCR7 * βCCR7+expXCR1 * βXCR1+expCX3CR1 * βCX3CR1 (exp=expression level; β=the regression coefficient derived from the multivariate Cox model). To plot the Kaplan-Meier curves in these sets, we classified the patients into low or high risk by the same cutoff point, based on the Youden index in the training set [21]. Survival differences between different risk groups were assessed and compared by the Kaplan-Meier estimate and log-rank test in the training, validation, and entire set. The time-dependent receiver operating characteristic (ROC) curve analysis for this 11-chemokine signature was performed for the prediction ability of OS within 48 months by using the "survival ROC" package. If the *p* values were less than 0.05, the log-rank test, Cox regression analysis, and ROC curve analysis were considered to be significant.

Gene functional analysis

To better understand the underlying function of these selected chemokines, the gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were analyzed using the Database for Annotation Visualization and Integrated Discovery (DAVID) [22].

Results

Identification and selection of potential chemokines in the training set

The research flow for the development of this prognostic signature is shown in Figure 1. Gene expression data of 46 chemokines were extracted from TCGA sequencing data, and we further fitted these 46 chemokines in the univariate Cox model for the training set (n=252, shown in Supplementary Table 1). Therefore, we identified 11 chemokines whose expressions were significantly correlated with OS (p<0.05, shown in Table 1). Among the 11 chemokines, the coefficients in univariate Cox regression of CCL2, CCL7, CXCL5, and CXCL7 in univariate Cox

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Table 1. The characteristics of 11 chemokines associated with overall survival in the training set of 252 HNSC patients (n=252, TCGA).

Gene symbol	Type	HR (95% CI)	Coefficients	p Value	Putative function
CCL2	Ligand	1.173	0.16	0.026	Risky
CCL7	Ligand	1.154	0.143	0.016	Risky
CCL22	Ligand	0.857	–0.154	0.03	Protective
XCL2	Ligand	0.856	–0.155	0.037	Protective
CXCL5	Ligand	1.113	0.107	0.01	Risky
CXCL8	Ligand	1.14	0.131	0.011	Risky
CCR4	Receptor	0.888	–0.119	0.025	Protective
CCR6	Receptor	0.772	–0.258	0.003	Protective
CCR7	Receptor	0.846	–0.167	0.005	Protective
XCR1	Receptor	0.831	–0.185	0.005	Protective
CX3CR1	Receptor	0.859	–0.152	0.025	Protective

CI – confidence index; HR – hazard ratio.

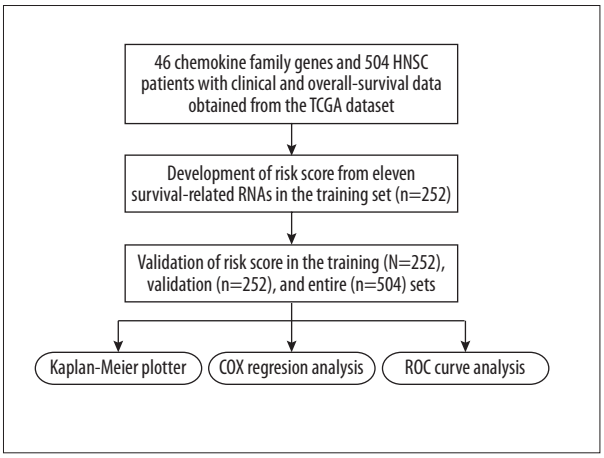

Figure 1. Study flow for the analysis of these survival-related chemokine genes.

model were positive, indicating that their higher levels of gene expression were associated with worse prognosis. In contrast, the coefficients of CCL22, XCL2, CCR4, CCR6, CCR7, XCR1, and CX3CR1 were negative, indicating that their higher levels of gene expression were associated with better prognosis.

Comparisons of survival between low-risk and high-risk groups

The entire study cohort of 504 patients was randomly grouped into training (n=252) and validation (n=252) sets. Based on these chemokines and their regression coefficients in the multivariate Cox model, we calculated the risk scores for each patient in the training (n=252), validation (n=252), and entire (n=504) sets (Figure 2). Using the cutoff value of risk scores (0.83074), HNSC patients were divided into a low-risk group and a high-risk group for training (low-risk/high-risk: 94/158) and validation (low-risk/high-risk: 58/194) sets. After integrating analysis of these 2 sets, there were 152 low-risk patients and 352 high-risk patients in the entire set (n=504). As shown in Figure 2, high-risk HNSC patients tended to have higher risk of death in the training, validation, and entire sets.

Table 2 lists the comprehensive clinical features of HNSC patients in the low-risk and high-risk groups. As shown in Figure 3A and Table 3, further validation of this 11-chemokine signature using Kaplan-Meier and log-rank analysis significantly predicted OS in the training [hazard ratio (HR)=3.497, 95% confidence interval (CI)=2.142–5.711, p<0.001], validation (HR=3.575, 95% CI=1.988–6.390, p<0.001), and entire (HR=3.324, 95% CI=2.363-4.939, p<0.001) sets. These results indicated that high-risk HNSC patients had significantly shorter OS than low-risk patients.

Multivariate Cox model

We further assessed whether this risk score was independent of these clinical factors (age, sex, clinical stage, and primary sites) by a multivariate Cox model. As shown in Table 4, this integrated 11-chemokine signature was identified as an independent prognostic factor in the training, validation, and entire sets (all p<0.001) for HNSC patients. Hence, our findings suggest that this integrated 11-chemokine signature may become a reliable and independent biomarker for the prediction of overall survival in HNSC patients.

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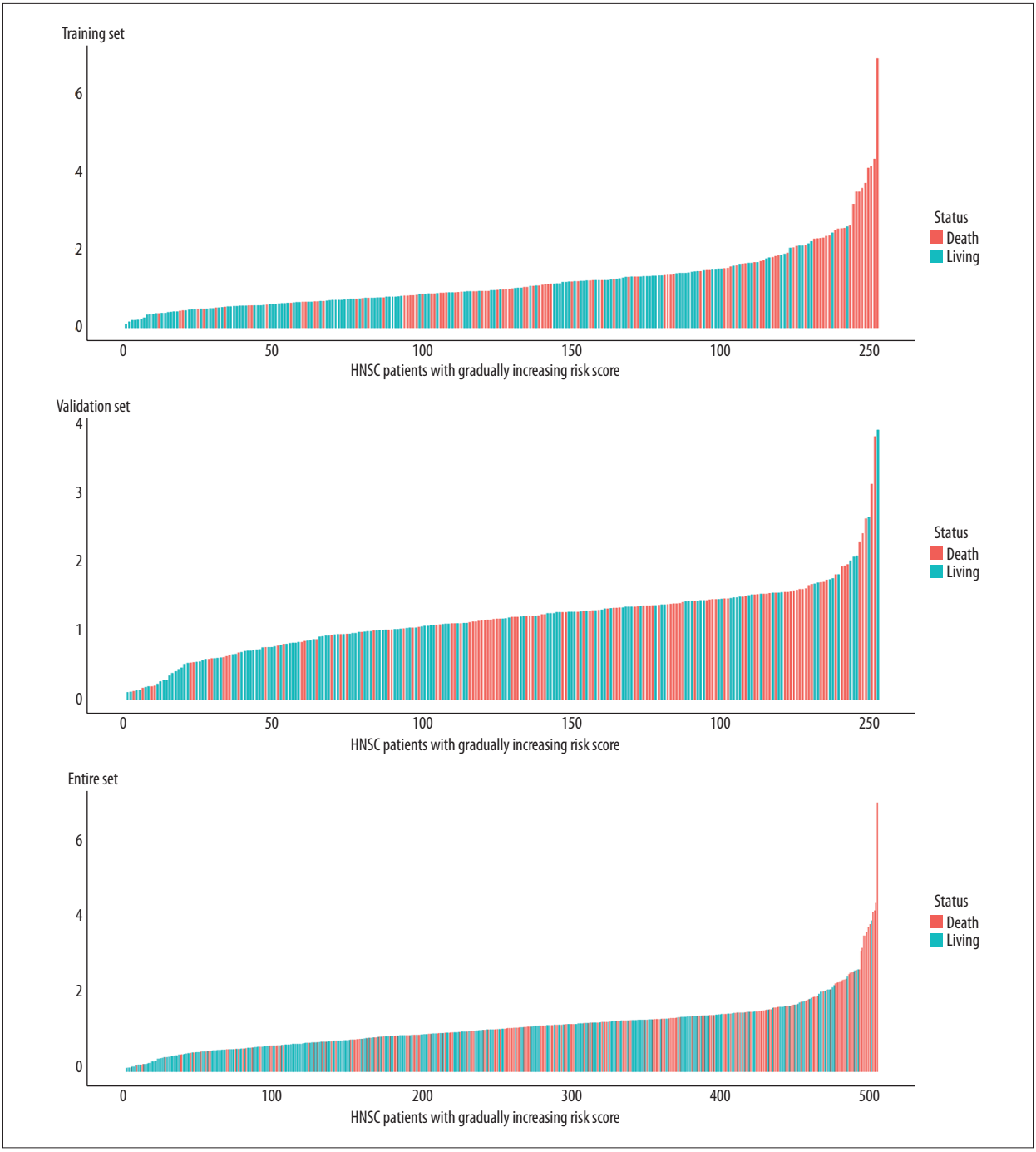

Figure 2. The distribution of risk score and overall survival status in the 3 datasets.

ROC curve analysis

As shown in Figure 3B, the AUC values for predicting overall survival within 48 months in the training, validation, and entire sets were 0.71, 0.69, and 0.69, respectively, highlighting the validity of this 11-chemokine signature.

Gene functional analysis

Gene functional analysis indicated 29 GO terms and 4 KEGG pathways which these 11 chemokines were enriched in (Figure 4A, 4B). The main 9 participating GO terms contained chemokine-mediated (GO: 0070098), inflammatory response (GO: 0006954), cellular response to interleukin-1 (GO: 00071347), neutrophil chemotaxis (GO: 0030593), cellular

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Table 2. Clinical characteristics of HNSC patients according to this 11-chemokine classifier in the training (n=252, TCGA), validation (n=252, TCGA), and entire (n=504, TCGA) sets.

Characteristics	Training set (n=252)			Validation set (n=252)			Entire set (n=504)		
	High-risk (n=158)	Low-risk (n=94)	p Value	High-risk (n=194)	Low-risk (n=58)	p Value	High-risk (n=352)	Low-risk (n=152)	p Value
Age									
<65y	96	65	0.180	132	41	0.703	228	106	0.279
≥65y	62	29		62	17		124	46	
Gender									
Male	114	71	0.557	144	42	0.518	258	113	0.807
Female	44	23		50	16		94	39	
Stage									
I–II	32	23	0.433	43	19	0.100	75	42	0.050
III–IV	126	71		151	39		277	110	
Primary sites									
Oral cavity	109	73	0.137	146	45	0.716	255	118	0.223
Pharynx and larynx	49	21		48	13		97	34	

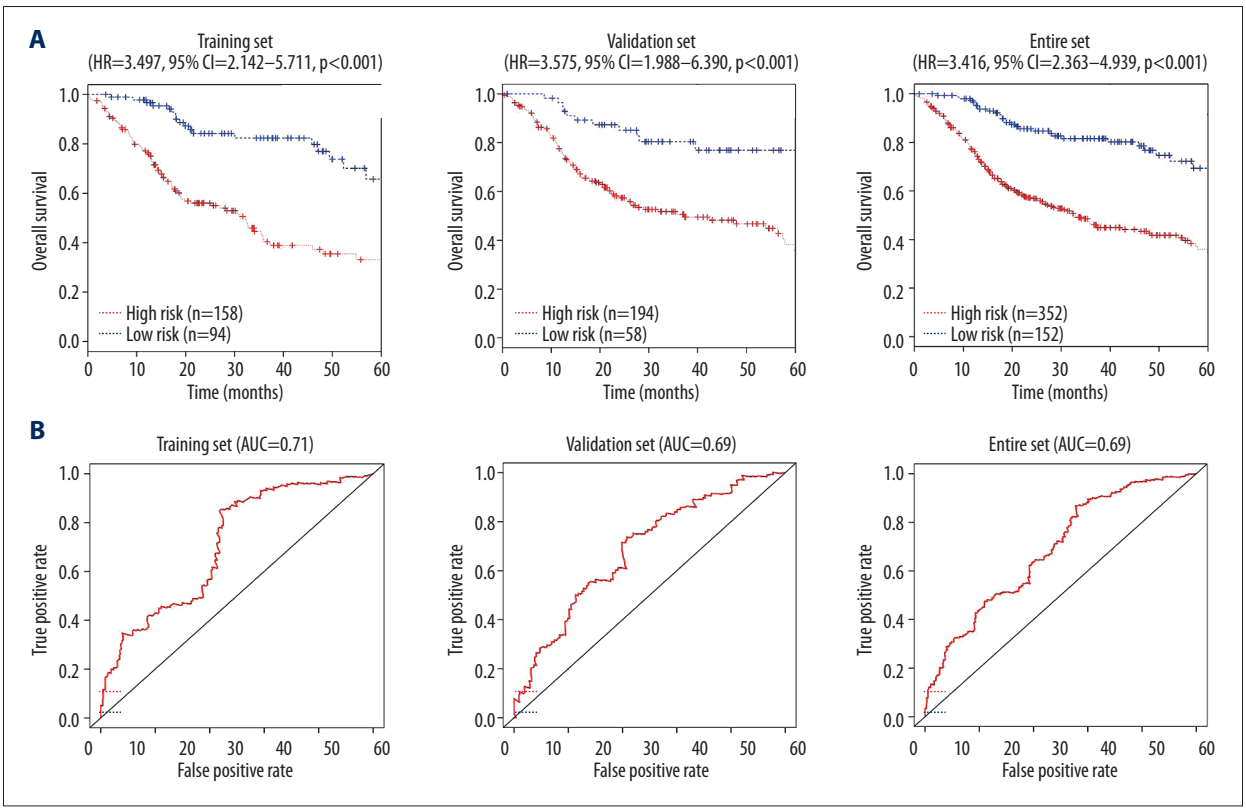

Figure 3. Identification and performance evaluation of these 11 chemokines signature in training, validation, and entire sets. (**A**) Kaplan-Meier survival curve analysis for overall survival of HNSC patients using the 11-chemokines signature in these 3 datasets. (**B**) ROC curve analysis of the 11-chemokines signature in these 3 datasets.

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Table 3. Log-rank test of overall survival according to this 11-ckemokine classifier in the training (n=252), validation (n=252), and entire (n=504) sets.

Datasets	Risk group (n)	Disease-free survival				
		1-year	3-year	5-year	HR (95% CI)	p. Value
Training set (n=252)	High-risk (n=158)	76.5%	40.4%	33.1%	3.497 (2.142-5.711)	<0.001
	Low-risk (n=94)	97.9%	82.3%	65.7%		
Validation set (n=252)	High-risk (n=194)	76.4%	50.7%	38.2%	3.575 (1.988-6.390)	<0.001
	Low-risk (n=58)	96.5%	80.6%	76.9%		
Entire set (n=504)	High-risk (n=352)	76.4%	46.1%	36.0%	3.416 (2.363-4.939)	<0.001
	Low-risk (n=152)	97.3%	81.6%	69.3%		

CI – confidence index; HR – hazard ratio.

Table 4. Multivariate Cox regression analysis of this eleven-chemokine classifier, gender, age, stage, and primary sites for overall survival in the training (n=252), validation (n=252), and entire (n=504) sets.

Datasets	Variable	Disease-free Survival	
		HR (95% CI)	p-Value
Training set (n=246)	The 11-chemokine classifier (high- *vs.* low-risk)	3.557 (2.165–5.845)	<0.001
	Age (≥65 years *vs.* <65 years)	1.562 (1.056–2.312)	0.026
	Gender (Female *vs.* Male)	1.66 (1.081–2.548)	0.021
	Tumor stage (II–IV *vs.* I–II)	0.999 (0.614–1.626)	0.998
	Primary sites (oral cavity *vs.* pharynx/larynx)	0.964 (0.617–1.505)	0.87
Validation set (n=246)	The eleven-chemokine classifier (high- *vs.* low-risk)	3.442 (1.919–6.172)	<0.001
	Age (≥65 years *vs.* <65 years)	1.009 (0.672–1.515)	0.97
	Gender (Female *vs.* Male)	1.065 (0.688–1.647)	0.78
	Tumor stage (II–IV *vs.* I–II)	1.226 (0.780–1.927)	0.38
	Primary sites (oral cavity *vs.* pharynx/larynx)	0.741 (0.462–1.188)	0.21
Entire set (n=504)	The eleven-chemokine classifier (high- *vs.* low-risk)	3.360 (2.320–4.867)	<0.001
	Age (≥65 years *vs.* <65 years)	1.250 (0.944–1.654)	0.117
	Gender (Female *vs.* Male)	1.301 (0.962–1.759)	0.088
	Tumor stage (II–IV *vs.* I–II)	1.097 (0.789–1.525)	0.579
	primary sites (oral cavity *vs.* pharynx/larynx)	0.860 (0.622–1.188)	0.361

HR – hazard ratio; NR – not reported; CI – confidence index.

response to tumor necrosis factor (GO: 0071356), lymphocyte chemotaxis (GO: 0048247), monocyte chemotaxis (GO: 0002548), chemokine activity (GO: 0008009), and CCR chemokine receptor (GO: 0048020). The key involved KEGG pathways were chemokine signaling pathway (Kegg: 04062), cytokine-cytokine receptor (Kegg: 04060), NOD-like receptor signaling pathway (Kegg: 04621), and Malaria (Kegg: 05144).

Discussion

Although the current tumor staging system has been used to define the risk stratification of HNSC for many years, it is inadequate at identifying high-risk HNSC patients [4,6,23,24]. Inconsistent clinical outcomes always existed among the same-stage patients with HNSC [5,25]. Many studies demonstrated that chemokine family genes play a pivotal role in tumor

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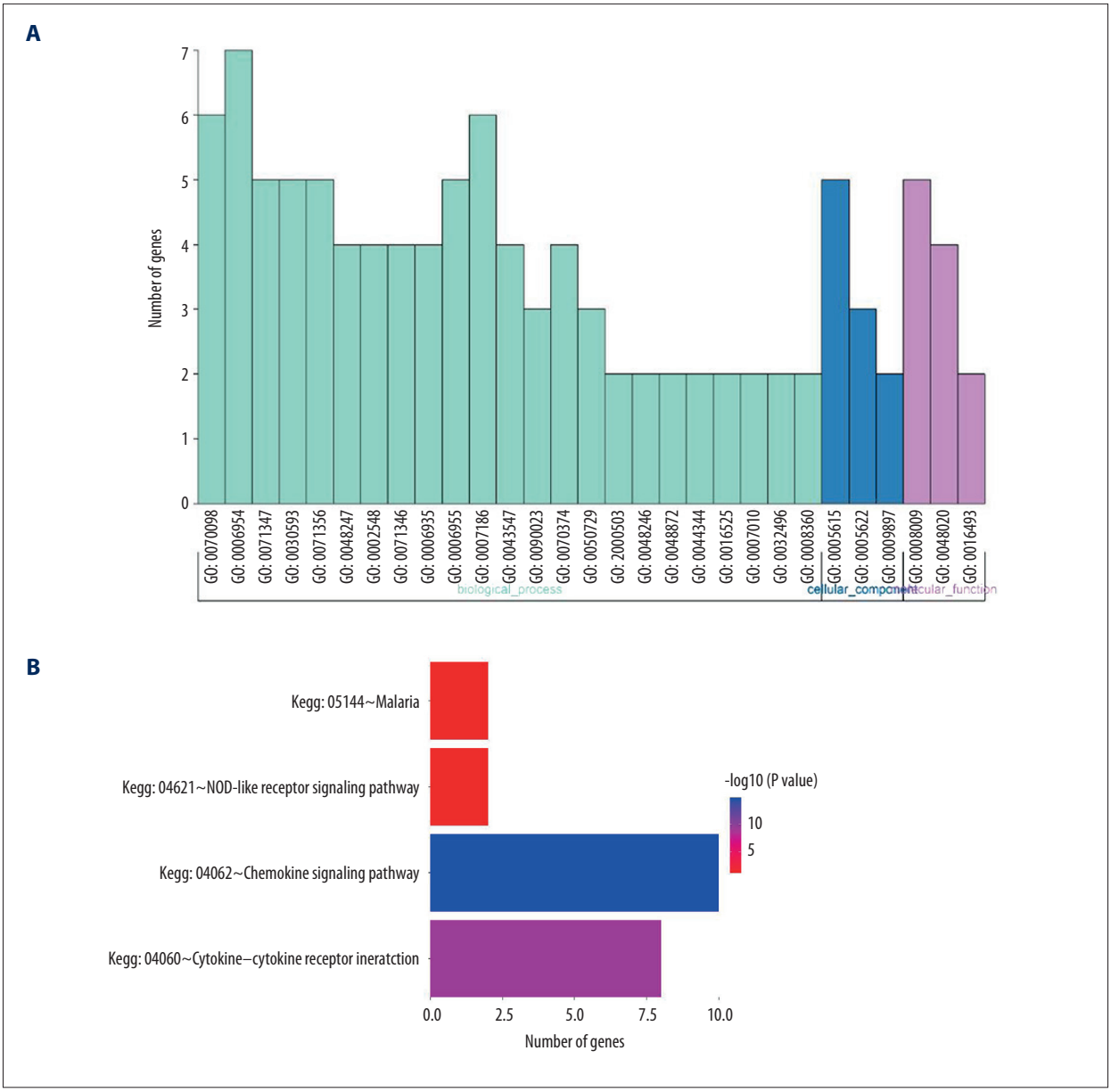

Figure 4. Gene function and pathway analysis. (**A**) GO enrichment analysis. (**B**) Significant pathway analysis.

inflammation, immunity, progression, and metastasis [26–29]. A multiple-gene prognostic biomarker of chemokine family genes is urgently needed and may contribute to the identification of potential HNSC patients with worse prognosis. To identify this multiple-gene prognostic biomarker, we profiled chemokine ligands and their receptors by mining the RNA sequencing data of TCGA. Based on the bioinformatic discovery and validation method, we constructed an 11-chemokine signature that can improve the prognostic prediction of overall survival in HNSC patients. The clinical utility of this signature can improve the predictive ability of the current staging system. In addition, the clinical application of this signature could classify patients with HNSC into low-risk and high-risk groups after radical surgery. High-risk patients with HNSC had worse prognosis than low-risk patients. This signature may be used as an additional biomarker for identifying potentially high-risk patients, which may contribute to personalized treatment for HNSC.

There are 7 protective genes (CCL22, XCL2, CCR4, CCR6, CCR7, XCR1, CX3CR1) and 4 risk genes (CCL2, CCL7, CXCL5, CXCL8) in this 11-chemokine signature. Previous research indicated that CCL2 and CCL7 are associated with tumor proliferation, invasion, migration, and tumor burden [30,31]. In HNSC cells, decreased CXCL5 expression inhibits cell proliferation and reduces cell migration and invasion *in vitro* and inhibits tumor formation

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in vivo [32]. CXCL8 is known to be a promoter of angiogenesis and a regulator of cell growth and motility in HNSC [33]. The serum level of CXCL8 was used to predict a lower survival rate in patients, because the chemokine promotes metastasis by neutrophil infiltration and stimulates vascular endothelial cell proliferation, survival, and migration [34–36].

Several studies found that CCR7 expression was significantly associated with nodal metastasis [37–40]. Tsujikawa et al. concluded that CCR4 expression in primary HNSCC cells may be an attractive diagnostic biomarker to predict lymph node metastasis and subsequent prognosis of HNSC patients [41]. However, levels of CCL22 in the peripheral blood have no correlation with tumor stage of HNSC [42]. A previous study showed that high expression of CCR7 was associated with disease-free survival and CCR4 was correlated with tumor site, showing higher immune-reactive scores in tumors of the oral cavity [24]. CCR6 and CCR7 mRNA levels were significantly decreased in lymph node (+) patients with laryngeal squamous cell carcinoma (LSCC) [43]. The prognostic effect of these remaining chemokines (XCL2, XCR1, and CX3CR1) in HNSC should be further explored.

We should acknowledge some potential limitations for this 11-chemokine signature. Firstly, gene enrichment analysis found that this 11-chemokine signature was mainly involved in 9 GO terms and 4 KEGG pathways., but the GO terms and KEGG pathways involved by these 11 chemokines were not confirmed by cell, animal, or clinical studies. Further studies may should be performed to provide potential therapeutic targets for HNSC. Secondly, only 46 chemokine family genes were selected for in this study. The connection between overall survival and mRNA levels of the remaining 14 chemokines should be studied by tumor specimens of HNSC furtherly. Thirdly, this 11-chemokine signature was constructed by a bioinformatic discovery and validation approach. This prognostic signature was not further verified by protein level data of Western blot or immunohistochemistry or RNA level data of quantitative reverse transcription polymerase chain reaction from clinical tumor specimens. Moreover, research in other databases is needed to verify the potential significance of this signature among different cohorts of HNSC patients.

Conclusions

We performed a comprehensive analysis of chemokines mRNA expression profiles and clinical data of HNSC patients in the TCGA database. Then, we identified an 11-chemokine signature that may improve the prediction of overall survival in HNSC patients. This is the first study to demonstrate the link between an 11-chemokine signature and overall survival in HNSC patients. Our results may support useful risk stratification of overall survival in HNSC patients, which would contribute to gene target treatment for HNSC. However, this 11-chemokine signature should be further tested by tumor specimens of HNSC before clinical application.

Conflict of interest

None.

Supplementary Table

Supplementary Table 1. Univariate Cox regression analysis of chemokine family genes associated with overall survival in the training set (n=252, TCGA).

Gene Symbol	Type	Sub-family	HR (95% CI)	Coefficient	p Value	Gene Symbol	Type	Sub-family	HR (95% CI)	Coefficient	p Value
CCL2	Ligand	CC	1.173 (1.019–1.351)	0.16	0.026	CXCL9	Ligand	CXC	0.966 (0.894–1.042)	–0.035	0.371
CCL3	Ligand	CC	1.13 (0.978–1.305)	0.122	0.097	CXCL10	Ligand	CXC	1.006 (0.935–1.082)	0.006	0.878
CCL7	Ligand	CC	1.154 (1.027–1.296)	0.143	0.016	CXCL11	Ligand	CXC	1.028 (0.957–1.103)	0.027	0.452
CCL11	Ligand	CC	1.024 (0.916–1.146)	0.024	0.671	CXCL12	Ligand	CXC	1.054 (0.923–1.204)	0.053	0.434
CCL13	Ligand	CC	1.07 (0.952–1.203)	0.068	0.256	CXCL14	Ligand	CXC	0.956 (0.881–1.036)	–0.045	0.274
CCL14	Ligand	CC	0.992 (0.897–1.097)	–0.008	0.876	CXCL16	Ligand	CXC	1.079 (0.823–1.415)	0.076	0.583

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Gene Symbol	Type	Sub-family	HR (95% CI)	Coefficient	p Value	Gene Symbol	Type	Sub-family	HR (95% CI)	Coefficient	p Value
CCL17	Ligand	CC	0.912 (0.796–1.044)	–0.092	0.183	CXCL17	Ligand	CXC	0.933 (0.867–1.004)	–0.069	0.064
CCL18	Ligand	CC	0.997 (0.896–1.109)	–0.003	0.954	CXCR1	Receptor	CXC	0.997 (0.904–1.098)	–0.003	0.945
CCL19	Ligand	CC	0.945 (0.875–1.021)	–0.056	0.153	CXCR2	Receptor	CXC	0.917 (0.824–1.019)	–0.087	0.108
CCL20	Ligand	CC	1.03 (0.948–1.12)	0.03	0.48	CXCR3	Receptor	CXC	0.909 (0.82–1.008)	–0.096	0.069
CCL21	Ligand	CC	0.928 (0.858–1.004)	–0.075	0.063	CXCR4	Receptor	CXC	0.871 (0.745–1.017)	–0.138	0.081
CCL22	Ligand	CC	0.857 (0.746–0.985)	–0.154	0.03	CXCR6	Receptor	CXC	0.886 (0.78–1.007)	–0.121	0.064
CCL23	Ligand	CC	1.079 (0.912–1.275)	0.076	0.375	XCL1	Ligand	XC	0.959 (0.85–1.083)	–0.041	0.503
CCL24	Ligand	CC	1 (0.876–1.143)	0	0.997	XCL2	Ligand	XC	0.856 (0.74–0.99)	–0.155	0.037
CCL27	Ligand	CC	1.014 (0.891–1.155)	0.014	0.83	XCR1	Receptor	XC	0.831 (0.73–0.946)	–0.185	0.005
CCL28	Ligand	CC	0.917 (0.801–1.049)	–0.087	0.207	CX3CL1	Ligand	CX3C	1.008 (0.904–1.124)	0.008	0.885
CCR1	Receptor	CC	1.07 (0.928–1.233)	0.067	0.352	CX3CR1	Receptor	CX3C	0.859 (0.752–0.981)	–0.152	0.025
CCR3	Receptor	CC	1.014 (0.816–1.261)	0.014	0.899	CXCL2	Ligand	CXC	1.062 (0.948–1.188)	0.06	0.299
CCR4	Receptor	CC	0.888 (0.8–0.985)	–0.119	0.025	CXCL3	Ligand	CXC	1.074 (0.965–1.196)	0.072	0.191
CCR6	Receptor	CC	0.772 (0.652–0.915)	–0.258	0.003	CXCL5	Ligand	CXC	1.113 (1.008–1.23)	0.107	0.01
CCR7	Receptor	CC	0.846 (0.752–0.951)	–0.167	0.005	CXCL6	Ligand	CXC	1.053 (0.966–1.148)	0.052	0.241
CCR8	Receptor	CC	0.961 (0.849–1.088)	–0.039	0.533	CXCL8	Ligand	CXC	1.14 (1.031–1.261)	0.131	0.011
CCR10	Receptor	CC	0.909 (0.785–1.052)	–0.096	0.201						

CI – confidence index; HR – hazard ratio.

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