

World Journal of *Clinical Cases*

World J Clin Cases 2022 November 26; 10(33): 12066-12461



MINIREVIEWS

- 12066** Review of risk factors, clinical manifestations, rapid diagnosis, and emergency treatment of neonatal perioperative pneumothorax
Zhang X, Zhang N, Ren YY

ORIGINAL ARTICLE**Clinical and Translational Research**

- 12077** Integrative analysis of platelet-related genes for the prognosis of esophageal cancer
Du QC, Wang XY, Hu CK, Zhou L, Fu Z, Liu S, Wang J, Ma YY, Liu MY, Yu H
- 12089** Comprehensive analysis of the relationship between cuproptosis-related genes and esophageal cancer prognosis
Xu H, Du QC, Wang XY, Zhou L, Wang J, Ma YY, Liu MY, Yu H
- 12104** Molecular mechanisms of Baihedihuang decoction as a treatment for breast cancer related anxiety: A network pharmacology and molecular docking study
Li ZH, Yang GH, Wang F
- 12116** Single-cell RNA-sequencing combined with bulk RNA-sequencing analysis of peripheral blood reveals the characteristics and key immune cell genes of ulcerative colitis
Dai YC, Qiao D, Fang CY, Chen QQ, Que RY, Xiao TG, Zheng L, Wang LJ, Zhang YL

Retrospective Study

- 12136** Diagnosis and treatment of tubal endometriosis in women undergoing laparoscopy: A case series from a single hospital
Jiao HN, Song W, Feng WW, Liu H
- 12146** Different positive end expiratory pressure and tidal volume controls on lung protection and inflammatory factors during surgical anesthesia
Wang Y, Yang Y, Wang DM, Li J, Bao QT, Wang BB, Zhu SJ, Zou L
- 12156** Transarterial chemoembolization combined with radiofrequency ablation in the treatment of large hepatocellular carcinoma with stage C
Sun SS, Li WD, Chen JL
- 12164** Coexistence of anaplastic lymphoma kinase rearrangement in lung adenocarcinoma harbouring epidermal growth factor receptor mutation: A single-center study
Zhong WX, Wei XF

Observational Study

- 12175** Prognostic values of optic nerve sheath diameter for comatose patients with acute stroke: An observational study
Zhu S, Cheng C, Wang LL, Zhao DJ, Zhao YL, Liu XZ
- 12184** Quality of care in patients with inflammatory bowel disease from a public health center in Brazil
Takamune DM, Cury GSA, Ferrás G, Herrerias GSP, Rivera A, Barros JR, Baima JP, Saad-Hossne R, Sasaki LY
- 12200** Comparison of the prevalence of sarcopenia in geriatric patients in Xining based on three different diagnostic criteria
Pan SQ, Li XF, Luo MQ, Li YM

Prospective Study

- 12208** Predictors of bowel damage in the long-term progression of Crohn's disease
Fernández-Clotet A, Panés J, Ricart E, Castro-Poceiro J, Masamunt MC, Rodríguez S, Caballol B, Ordás I, Rimola J

Randomized Controlled Trial

- 12221** Protective effect of recombinant human brain natriuretic peptide against contrast-induced nephropathy in elderly acute myocardial infarction patients: A randomized controlled trial
Zhang YJ, Yin L, Li J

META-ANALYSIS

- 12230** Prognostic role of pretreatment serum ferritin concentration in lung cancer patients: A meta-analysis
Gao Y, Ge JT

CASE REPORT

- 12240** Non-surgical management of dens invaginatus type IIIB in maxillary lateral incisor with three root canals and 6-year follow-up: A case report and review of literature
Arora S, Gill GS, Saquib SA, Saluja P, Baba SM, Khateeb SU, Abdulla AM, Bavabeedu SS, Ali ABM, Elagib MFA
- 12247** Unusual presentation of Loeys-Dietz syndrome: A case report of clinical findings and treatment challenges
Azrad-Daniel S, Cupa-Galvan C, Farca-Soffer S, Perez-Zincer F, Lopez-Acosta ME
- 12257** Peroral endoscopic myotomy assisted with an elastic ring for achalasia with obvious submucosal fibrosis: A case report
Wang BH, Li RY
- 12261** Subclavian brachial plexus metastasis from breast cancer: A case report
Zeng Z, Lin N, Sun LT, Chen CX
- 12268** Case mistaken for leukemia after mRNA COVID-19 vaccine administration: A case report
Lee SB, Park CY, Park SG, Lee HJ
- 12278** Orthodontic-surgical treatment of an Angle Class II malocclusion patient with mandibular hypoplasia and missing maxillary first molars: A case report
Li GF, Zhang CX, Wen J, Huang ZW, Li H

- 12289** Multiple cranial nerve palsies with small angle exotropia following COVID-19 mRNA vaccination in an adolescent: A case report
Lee H, Byun JC, Kim WJ, Chang MC, Kim S
- 12295** Surgical and nutritional interventions for endometrial receptivity: A case report and review of literature
Hernández-Melchor D, Palafox-Gómez C, Madrazo I, Ortiz G, Padilla-Viveros A, López-Bayghen E
- 12305** Conversion therapy for advanced penile cancer with tislelizumab combined with chemotherapy: A case report and review of literature
Long XY, Zhang S, Tang LS, Li X, Liu JY
- 12313** Endoscopic magnetic compression stricturoplasty for congenital esophageal stenosis: A case report
Liu SQ, Lv Y, Luo RX
- 12319** Novel *hydroxymethylbilane synthase* gene mutation identified and confirmed in a woman with acute intermittent porphyria: A case report
Zhou YQ, Wang XQ, Jiang J, Huang SL, Dai ZJ, Kong QQ
- 12328** Modified fixation for periprosthetic supracondylar femur fractures: Two case reports and review of the literature
Li QW, Wu B, Chen B
- 12337** Erbium-doped yttrium aluminum garnet laser and advanced platelet-rich fibrin+ in periodontal diseases: Two case reports and review of the literature
Tan KS
- 12345** Segmental artery injury during transforaminal percutaneous endoscopic lumbar discectomy: Two case reports
Cho WJ, Kim KW, Park HY, Kim BH, Lee JS
- 12352** Pacemaker electrode rupture causes recurrent syncope: A case report
Zhu XY, Tang XH, Huang WY
- 12358** Hybrid intercalated duct lesion of the parotid: A case report
Stankevicius D, Petroska D, Zaleckas L, Kutanovaite O
- 12365** Clinical features and prognosis of multiple myeloma and orbital extramedullary disease: Seven cases report and review of literature
Hu WL, Song JY, Li X, Pei XJ, Zhang JJ, Shen M, Tang R, Pan ZY, Huang ZX
- 12375** Colon mucosal injury caused by water jet malfunction during a screening colonoscopy: A case report
Patel P, Chen CH
- 12380** Primary malignant pericardial mesothelioma with difficult antemortem diagnosis: A case report
Oka N, Orita Y, Oshita C, Nakayama H, Teragawa H
- 12388** Typical imaging manifestation of neuronal intranuclear inclusion disease in a man with unsteady gait: A case report
Gao X, Shao ZD, Zhu L

- 12395** Multimodality imaging and treatment of paranasal sinuses nuclear protein in testis carcinoma: A case report
Huang WP, Gao G, Qiu YK, Yang Q, Song LL, Chen Z, Gao JB, Kang L
- 12404** T1 rectal mucinous adenocarcinoma with bilateral enlarged lateral lymph nodes and unilateral metastasis: A case report
Liu XW, Zhou B, Wu XY, Yu WB, Zhu RF
- 12410** Influence of enhancing dynamic scapular recognition on shoulder disability, and pain in diabetics with frozen shoulder: A case report
Mohamed AA
- 12416** Acute myocardial necrosis caused by aconitine poisoning: A case report
Liao YP, Shen LH, Cai LH, Chen J, Shao HQ
- 12422** Danggui Sini decoction treatment of refractory allergic cutaneous vasculitis: A case report
Chen XY, Wu ZM, Wang R, Cao YH, Tao YL
- 12430** Phlegmonous gastritis after biloma drainage: A case report and review of the literature
Yang KC, Kuo HY, Kang JW
- 12440** Novel *TINF2* gene mutation in dyskeratosis congenita with extremely short telomeres: A case report
Picos-Cárdenas VJ, Beltrán-Ontiveros SA, Cruz-Ramos JA, Contreras-Gutiérrez JA, Arámbula-Meraz E, Angulo-Rojo C, Guadrón-Llanos AM, Leal-León EA, Cedano-Prieto DM, Meza-Espinoza JP
- 12447** Synchronous early gastric and intestinal mucosa-associated lymphoid tissue lymphoma in a *Helicobacter pylori*-negative patient: A case report
Lu SN, Huang C, Li LL, Di LJ, Yao J, Tuo BG, Xie R

LETTER TO THE EDITOR

- 12455** Diagnostic value of metagenomics next-generation sequencing technology in disseminated strongyloidiasis
Song P, Li X
- 12458** Diagnostic value of imaging examination in autoimmune pancreatitis
Wang F, Peng Y, Xiao B

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Cornelia Bala, MD, PhD, Professor, Department of Diabetes and Nutrition Diseases, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca 400006, Romania. cbala@umfcluj.ro

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xiang Li*; Editorial Office Director: *Jin-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

November 26, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Clinical and Translational Research

Integrative analysis of platelet-related genes for the prognosis of esophageal cancer

Qian-Cheng Du, Xin-Yu Wang, Cheng-Kai Hu, Ling Zhou, Zheng Fu, Shun Liu, Jian Wang, Ying-Ying Ma, Meng-Yao Liu, Hua Yu

Specialty type: Surgery

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): E

P-Reviewer: Endo S, Japan; Micsik T, Hungary; Rasoulinejad A, Egypt

Received: May 7, 2022

Peer-review started: May 7, 2022

First decision: July 13, 2022

Revised: August 15, 2022

Accepted: October 11, 2022

Article in press: October 11, 2022

Published online: November 26, 2022



Qian-Cheng Du, Cheng-Kai Hu, Zheng Fu, Shun Liu, Jian Wang, Ying-Ying Ma, Meng-Yao Liu, Department of Thoracic Surgery, Shanghai Xuhui Central Hospital, Shanghai 200031, China

Xin-Yu Wang, Ling Zhou, Hua Yu, Department of General Surgery, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, Shanghai 200434, China

Corresponding author: Hua Yu, MM, Associate Chief Physician, Department of General Surgery, Shanghai Fourth People's Hospital, School of Medicine, Tongji University, No. 1279 Sanmen Road, Hongkou District, Shanghai 200434, China. luckyyuhua@163.com

Abstract

BACKGROUND

Every year, esophageal cancer is responsible for 509000 deaths and around 572000 new cases worldwide. Although esophageal cancer treatment options have advanced, patients still have a dismal 5-year survival rate.

AIM

To investigate the relationship between genes associated to platelets and the prognosis of esophageal cancer.

METHODS

We searched differentially expressed genes for changes between 151 tumor tissues and 653 normal, healthy tissues using the "limma" package. To develop a prediction model of platelet-related genes, a univariate Cox regression analysis and least absolute shrinkage and selection operator Cox regression analysis were carried out. Based on a median risk score, patients were divided into high-risk and low-risk categories. A nomogram was created to predict the 1-, 2-, and 3-year overall survival (OS) of esophageal cancer patients using four platelet-related gene signatures, TNM stages, and pathological type. Additionally, the concordance index, receiver operating characteristic curve, and calibration curve were used to validate the nomogram.

RESULTS

The prognosis of esophageal cancer was associated to *APOOL*, *EP300*, *PLA2G6*, and *VAMP7* according to univariate Cox regression analysis and least absolute shrinkage and selection operator regression analysis. Patients with esophageal cancer at high risk had substantially shorter OS than those with cancer at low risk,

according to a Kaplan-Meier analysis ($P < 0.05$). TNM stage (hazard ratio: 2.187, 95% confidence interval: 1.242-3.852, $P = 0.007$) in both univariate and multivariate Cox regression and risk score were independently correlated with OS (hazard ratio: 2.451, 95% confidence interval: 1.599-3.756, $P < 0.001$).

CONCLUSION

A survival risk score model and independent prognostic variables for esophageal cancer have been developed using *APOOL*, *EP300*, *PLA2G6*, and *VAMP7*. OS for esophageal cancer might be predicted using the nomogram based on TNM stage, pathological type, and risk score. The nomogram demonstrated strong predictive ability, as shown by the concordance index, receiver operating characteristic curve, and calibration curve.

Key Words: Esophageal cancer; Platelet; Gene signature; Overall survival; Nomogram

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Esophageal cancer is one of the most prevalent cancers. Despite significant improvements in esophageal cancer therapy over the past several years, the survival rates of patients with the malignancy are still extremely low. Numerous studies have demonstrated the important role platelets play in the initiation and growth of tumors. The precise underlying biological processes of platelet-related genes in esophageal cancer are unknown. An efficient risk score model based on the platelet-related genes may accurately predict the survival of patients with esophageal cancer, helping to clarify the relationship between platelet-related genes and the prognosis of the disease.

Citation: Du QC, Wang XY, Hu CK, Zhou L, Fu Z, Liu S, Wang J, Ma YY, Liu MY, Yu H. Integrative analysis of platelet-related genes for the prognosis of esophageal cancer. *World J Clin Cases* 2022; 10(33): 12077-12088

URL: <https://www.wjgnet.com/2307-8960/full/v10/i33/12077.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v10.i33.12077>

INTRODUCTION

Esophageal cancer incidence is increasing globally, and western countries have a higher prevalence of adenocarcinomas. Over 95% of esophageal cancer patients in China are diagnosed with esophageal squamous cell carcinomas; males are more likely than females to have this kind of cancer[1]. The 5-year survival rate for esophageal cancer patients is a little less than 20% despite improvements in therapy[2]. Target therapy and immunotherapy have made significant advancements in the treatment of esophageal cancer, although only some patients may benefit from them. Therefore, biomarkers to guide therapy and predict prognosis are urgently needed for patients with esophageal cancer.

In recent years, several attempts have been undertaken to better forecast the biology of each individual in esophageal cancer and to find prognostic and predictive biomarkers. Despite this, individuals with esophageal cancer often have a dismal prognosis because there are currently no reliable biomarkers for prognosis prediction and early identification.

Platelets may help tumor cells escape the immune system if they abnormally concentrate in the peripheral circulation and survive for prolonged periods of time. Platelet-derived growth factors, such as platelet factor 4, thrombospondin, and vascular endothelial growth factor, aid in the adhesion, invasion, angiogenesis, and tumor development of hematogenous cancer[3]. These findings suggest that platelets may be crucial in the growth of tumors in a variety of cancer types. Platelet research is mostly focused on the relationship between platelet characteristics and the prognosis of malignant tumors[4,5]. It may be possible to find novel treatment targets and improve the prognosis of malignant tumors by better understanding platelet-related genes and the underlying processes.

The link between platelet-related genes and survival in esophageal cancer patients has never been addressed, and only a small number of studies have looked at this relationship. This study examined the expression patterns of platelet-related genes and their prognostic significance in esophageal cancer by bioinformatics analysis. Finally, using pathway enrichment analysis to uncover probable biological roles for the platelet-related gene signature, we further investigated its function.

MATERIALS AND METHODS

Animals were not used in the study nor were there any human participants, data, or tissue. A public database served as the source for all the data.

Data collection

The Cancer Genome Atlas website at <https://portal.gdc.cancer.gov/> allows users to obtain clinical and gene expression data of patients with esophageal cancer. Gene expression levels in normal tissue samples were extracted using Genotype-Tissue Expression databases (<https://xenabrowser.net/>). Using the “limma” package in R, raw data is normalized before further data processing. With the term “platelet” as the target keyword, 369 genes with a connection to platelets were found in AmiGO 2 (<http://amigo.geneontology.org/>).

Identification of differentially expressed and prognostic genes

Using the “limma” package and the Wilcoxon signed-rank test in the R project, we found platelet-related genes that were differentially expressed between esophageal cancer and the healthy control group. By utilizing log fold change > 1 and false discovery rates < 0.05 as criteria, differentially expressed genes (DEGs) were chosen. The univariate Cox regression tests were used to evaluate the prognostic implications of overall survival (OS) for esophageal cancer. The intersection of DEGs and prognostic genes yielded the DEGs associated with the prognosis of esophageal cancer. Additionally, prospective risk factors based on genes connected to platelets were developed using least absolute shrinkage and selection operator Cox regression using the package “glmnet.” The penalty regularization parameter lambda (λ) was established using ten-fold cross validation, and we selected the value where the partial likelihood deviance was the minimum in order to prevent overfitting effects in the model. We generated the risk score using the following formula: risk score[6] = $\sum_{\text{genes}} \text{Cox coefficient} \times \text{genes expression levels}$. Then, based on their median risk ratings, patients were divided into high-risk and low-risk groups.

Principal component analysis and t-distributed stochastic neighbor embedding

Using the R function “prcomp” from the “stats” package, principal component analysis was performed on each set of data. Additionally, the R package “Rtsne” was utilized to create the t-distributed stochastic neighbor embedding approach in order to visualize clustering. The optimal cutoffs for the survival analysis of each gene were determined using the “surv cutpoint” function of the “survminer” R package. Finally, a software package called “survival operating characteristic (ROC)” was adopted to analyze the time-dependent ROC curve in order to evaluate the gene signature’s predictive ability for time-dependent cancer mortality.

Function enrichment analysis

We used the “ClusterProfiler” R package to distinguish between the functional pathways enriched by the DEGs in the high-risk and low-risk groups based on Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Additionally, results from expression analysis and functional annotation enrichment analysis were displayed using the GO Circle and GO Chord plot methods in the “GO plot” R package.

Establishment of the nomogram

With the use of prognostic gene signatures and a combination of clinicopathological factors, we developed a nomogram to predict each person’s probability of survival. Performance of the nomogram was evaluated using calibration plots and the concordance index. The dotted 45-degree line on the calibration graph represented the ideal forecast, while the X- and Y-axes on the graph represented the nomogram-predicted progression and the observed outcome, respectively. The model’s performance was assessed using a bootstrapping approach, which could compensate for overly optimistic assumptions.

Statistical analysis

R (version 4.1.0, <http://www.r-project.org/>) was used to perform the statistical analysis. The gene expression in tumor tissues and healthy control tissues was compared using the Student’s *t* test. The Fisher’s exact test or the χ^2 test, as applicable, were used to compare proportions. The Kaplan-Meier method was also used to assess progression-free survival and OS using log-rank testing. Univariate and multivariate Cox proportional hazard regression analyses were used to identify OS independent factors. Less than 0.05 was considered statistically significant for two-tailed *P* values.

RESULTS

We recruited 653 healthy individuals as controls and 151 patients with esophageal cancer as the case

group. The Cancer Genome Atlas database contained details on 151 esophageal cancer cases, whereas the Genotype-Tissue Expression database contained information on 653 healthy controls. All information came from freely accessible public databases. The clinical characteristics of 151 esophageal cancer patients are summarized in [Table 1](#).

Identification of prognostic platelet-related DEGs

We discovered 144 DEGs when comparing the case group to the healthy control group, of which 77 genes were upregulated and 67 genes were downregulated ([Figure 1A](#)). Using univariate Cox proportional regression analysis for 369 platelet-related genes, we identified 9 platelet-related prognostic genes, including *AP3D1*, *APOOL*, *CYRIB*, *DDIT3*, *EP300*, *HPS4*, *PLA2G6*, *TMSB4X*, and *VAMP7*, as being substantially correlated with OS ([Figure 1B](#), $P < 0.05$). We utilized a Venn diagram to discover the intersection between DEGs and platelet-related prognostic genes in order to further select platelet-related DEGs. The findings demonstrate that four genes, including *APOOL*, *EP300*, *PLA2G6* and *VAMP7*, were connected to esophageal cancer prognosis ([Figure 1C](#)).

Establishment of prognostic risk model

Additionally, we utilized the least absolute shrinkage and selection operator Cox analysis to choose the top four prognostic biomarkers, including *APOOL*, *EP300*, *PLA2G6*, and *VAMP7*, and we subsequently developed a classifier for predicting survival based on the four platelet-related prognostic genes ([Figure 2A and B](#), [Table 2](#)). The formula used was: risk score = $0.739 \times$ expression level of *APOOL* - $0.801 \times$ expression level of *EP300* - $0.674 \times$ expression level of *PLA2G6* + $0.798 \times$ expression level of *VAMP7*. Using the aforementioned formula, we calculated the risk scores for each sample. The median risk score was then used to classify the patients into low-risk and high-risk categories. The distributions of the high- and low-risk groups were marginally dispersed, according to the t-distributed stochastic neighbor embedding analysis ([Figure 2C](#)). The expression of the four platelet-related genes was used to compare the differences between the low- and high-risk groupings using principal component analysis ([Figure 2D](#)). In conclusion, high-risk and low-risk groups can be easily distinguished by the predictive characteristics of platelet-related genes.

Correlation between risk model and clinicopathologic characteristics

To ascertain if our risk score model correlated with clinicopathological parameters, squamous cell carcinoma and adenocarcinoma were examined as two clinicopathological findings. A similar outcome was shown in subgroups of adenocarcinoma and squamous cell carcinoma as a same consequence of the evaluation between subgroups and the entire population ([Figure 2E, F, and G](#)). In contrast to *PLA2G6* and *EP300*, which were strongly expressed in the low-risk group, *APOOL* and *VAMP7* were substantially expressed in the high-risk group. Age, sex, grade, and stage were clinical factors that did not differ between the high- and low-risk groups in our research. However, there were still notable variances between the various pathological categories of the two groups. Patients with adenocarcinoma had a comparatively high-risk score ([Table 3](#)).

Prognostic value of risk score for OS

[Figure 3A and B](#) show that patient survival times decreased as risk ratings rose, and largely all of the patients who passed away belonged to the high-risk category. The prognostic significance of DEGs in esophageal cancer was assessed using Kaplan-Meier survival analysis ([Figure 3C](#)). Patient prognoses were considerably poorer in the high-risk group than in the low-risk group ($P < 0.001$). Additionally, the univariate Cox regression analysis was carried out to determine the prognostic significance of the features ([Figure 3D](#)). The stage and risk score were statistically significant ($P < 0.001$), while the individuals' age, sex, and pathological type had no statistically significant impact on their survival. Furthermore, the multivariate analysis revealed that the stage and risk score were independent risk factors for OS ([Figure 3E](#)). The area under the curve (AUC) for survival after 1, 2, and 3 years using ROC analysis was 0.620, 0.750, and 0.790, respectively ([Figure 3F](#)). In other words, the platelet-related gene signature offered useful predictive value with clinical relevance for appropriately classifying OS patients.

Functional enrichment analysis of platelet-related genes

GO enrichment analysis revealed ten significantly enriched pathways, including those that control neuron death, cell growth, response to cytokine stimulus, positive regulation of phosphorylation, positive regulation of intracellular protein transport, positive regulation of cellular protein localization, positive regulation of intracellular transport, and regulation of cytokine-mediated signaling pathway ([Figure 4A](#)). "Neuron death" is a biological process word with the greatest richness (GO: 0070997). Platinum drug resistance was the most enriched and important route, according to KEGG analysis. Additionally, apoptosis was significantly enriched ([Figure 4B](#)).

Table 1 Clinical characteristics of all esophageal cancer patients

Variables	Esophageal cancer	Percent
Age in yr		
≤ 65	94	62.3
> 65	57	37.7
Sex		
Male	129	85.4
Female	22	14.6
Stage		
I	18	11.9
II	70	46.4
III	51	33.8
IV	12	7.9
Grade		
G1	16	10.6
G2	60	39.7
G3	41	27.2
Gx	34	22.5
Alcohol consumption		
Yes	105	69.5
No	43	28.5
Unknown	3	2.0
Symptoms		
Yes	116	76.8
No	10	6.6
Unknown	25	16.6
Pathological type		
Squamous cell carcinoma	77	51.0
Adenocarcinoma	74	49.0
Survival status		
Alive	93	61.6
Deceased	58	38.4
Smoking-yrs	38.5 (30.0-50.0)	
BMI	24.4 (21.2-27.4)	
Mean follow-up time in mo	13.4 (7.7-23.1)	

BMI: Body mass index.

Nomogram construction based on 4-gene signature

As previously mentioned, statistical analysis showed that the two independent prognostic indicators linked to OS were TNM stage and risk score. In order to eliminate pathological type interference, two pathological types were added to the nomogram. Finally, to predict the prognosis of esophageal cancer more accurately, we created a novel prognostic nomogram based on TNM stage, pathological type, and risk score (Figure 5A). The nomogram was used to evaluate each patient's probability of survival, and the ROC curve was used to assess how well the nomogram predicted outcomes. In 1-, 2-, and 3-year intervals, this nomogram's AUC was 0.722, 0.831, and 0.843, respectively (Figure 5B). The nomogram's

Table 2 Platelet-related genes in the prognostic classifier associated with overall survival

Gene	Univariate Cox regression analysis			LASSO
	HR	95%CI	P	Coefficient
PLA2G6	0.581	0.343-0.983	0.040	-0.674
EP300	0.543	0.301-0.981	0.040	-0.801
APOOL	1.967	1.186-3.262	0.008	0.739
VAMP7	2.452	1.269-4.740	0.008	0.798

HR: Hazard ratio; CI: Confidence interval; LASSO: Least absolute shrinkage and selection operator.

Table 3 Correlations between risk score of the platelet-related genes and clinicopathological characteristics

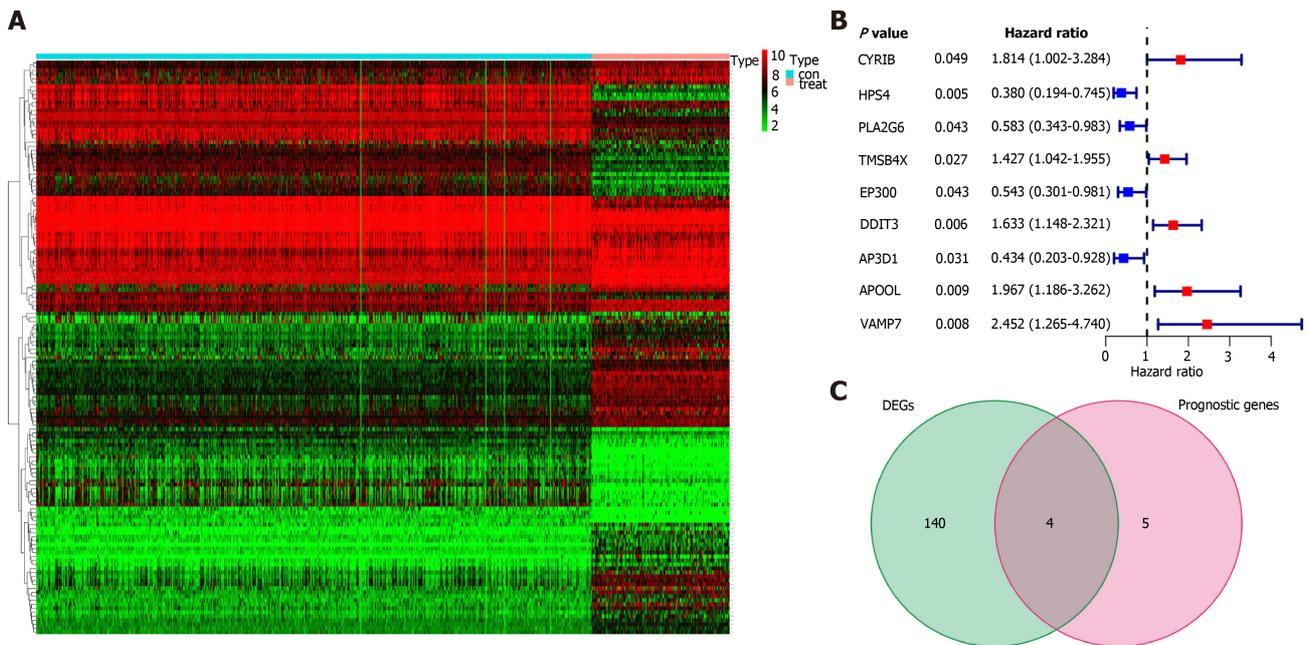
Parameters	Risk model		χ^2	P
	High risk	Low risk		
Age in yr			0.321	0.571
≤ 65	45	49		
> 65	30	27		
Sex			1.824	0.177
Male	67	62		
Female	8	14		
Grade			0.188	0.910
G1-2	37	39		
G3	20	21		
Gx	18	16		
Histological type			4.134	0.042
Squamous cell carcinoma	32	45		
Adenocarcinoma	43	31		
Stage			2.416	0.120
I-II	39	49		
III-IV	36	27		

calibration curves for the probabilities of 1-, 2-, and 3-year survival demonstrated good agreement between prediction and observation (Figure 5C). The nomogram's Harrell's concordance index value was 0.729. After additional verification, our nomogram performed quite well.

DISCUSSION

Esophageal cancer is mostly an aging illness, peaking in incidence in the eighth decade of life, and the global elderly population is expanding quickly[7]. Even after full resection of esophageal cancer, the prognosis remains dismal despite advancements in multimodal treatments that integrate surgery, chemotherapy, radiation, and chemoradiotherapy[8]. The main treatment for early esophageal cancer was surgical resection; however, patients who had recurrence or progression of the cancer had a difficult time getting treatment[9]. Although tumor grade offers useful prognostic information, other trustworthy factors are required for more accurate prognosis prediction.

In terms of incidence, esophageal cancer is the eighth most common cancer worldwide, and it is the sixth most lethal[10]. The majority of those affected by this illness are elderly, and the average age of diagnosis is becoming older, peaking between 70-years-old and 75-years-old[11]. However, there were no age differences between the high-risk and low-risk esophageal cancer groups in our study.



DOI: 10.12998/wjcc.v10.i33.12077 Copyright ©The Author(s) 2022.

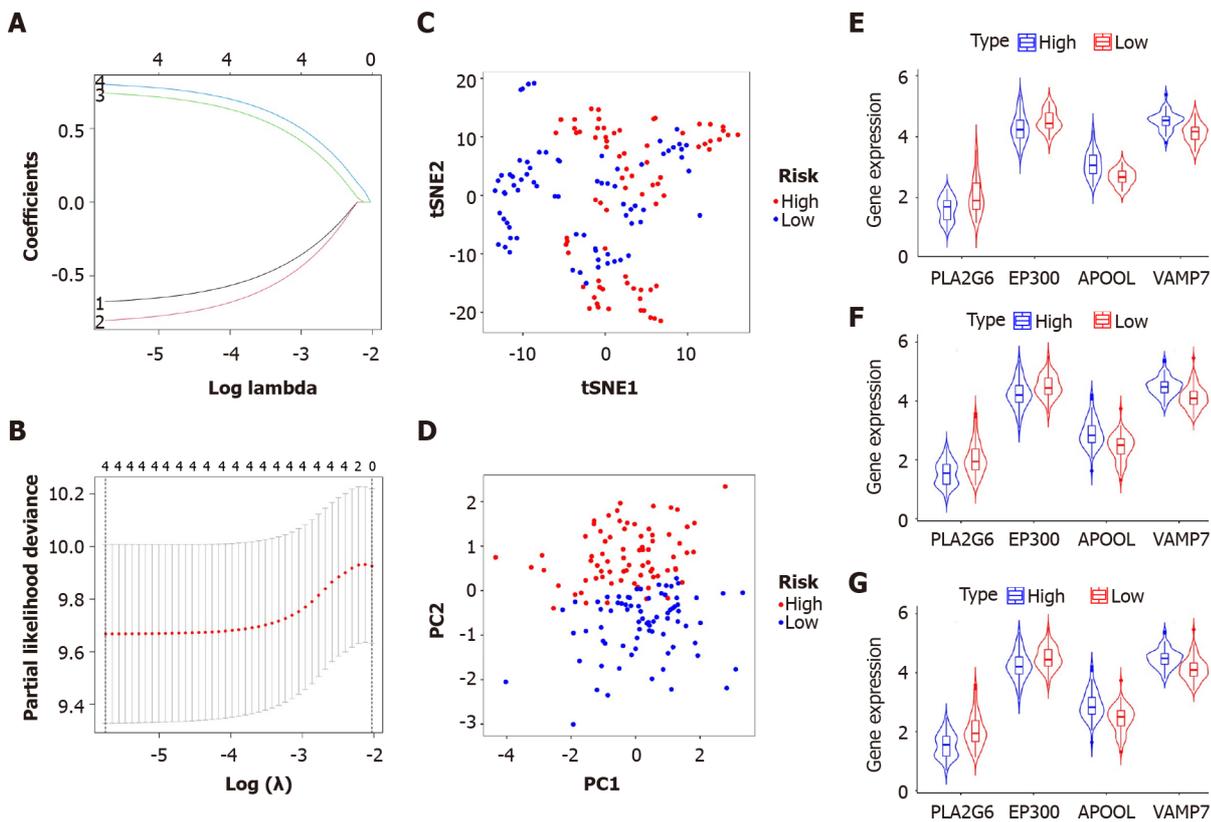
Figure 1 Identification of the candidate platelet-related genes in the esophageal cancer cohort. A: The heat map showed the expression of 369 platelet-related genes in healthy normal tissues and tumor tissues; B: Forest plots showed the results of the univariate Cox regression analysis between gene expression and overall survival; C: Venn diagram was used to identify differentially expressed genes between tumor and healthy normal tissue that were correlated with overall survival. DEGs: Differentially expressed genes.

Numerous forms of solid tumors typically exhibit platelet-related characteristics, which are essential to the development and growth of tumors[12,13]. Platelets help tumor cells grow, survive, and migrate [14]. To shield tumor cells from immune responses, platelets may form complexes with tumor cells[15]. Conversely, tumor cells are known to both activate platelets and cause platelet aggregation[12]. These mechanisms of tumor cell-platelet interactions, however, are still poorly understood. In order to further investigate the relationship between platelets and esophageal cancer, 369 platelet-related genes were included. By using univariate Cox and multivariate Cox analysis, four differentially expressed prognostic genes were identified, and a prognostic risk model based on a four platelet-related gene signature was established.

Four gene signatures have been discovered in this study utilizing univariate Cox regression analysis and the least absolute shrinkage and selection operator Cox regression model to predict OS for esophageal cancer. Additionally, 151 patients with esophageal cancer were divided into high- and low-risk groups based on the median risk model score using gene expression data. The prognosis between the high-risk group and the low-risk group differed significantly. As a result, the risk score method can accurately predict the results of esophageal cancer samples. GO and KEGG analyses were used to analyze biological processes and pathways in order to better investigate the mechanisms behind our risk model. Analyses of GO and KEGG data revealed that the majority of GO and KEGG enrichments were related to carcinogenesis and development. The risk model contained the four genes *APOOL*, *EP300*, *PLA2G6* and *VAMP7*. While the expression levels of *EP300* and *PLA2G6* were positively connected with prognosis, the expression levels of *APOOL* and *VAMP7* were adversely correlated with esophageal cancer.

According to Zhu *et al*[16], *VAMP7* is implicated in the promotion of tumors since it is upregulated in high-risk individuals. Poor prognosis for esophageal squamous carcinoma was linked to *EP300* epitopes as an oncogene[17]. The *EP300* oncogene promotes tumor development, as was shown in earlier research *in vitro* using esophageal squamous cell carcinoma cell lines[17]. Studies on lung, colon, prostate, bladder, and breast cancer have also demonstrated this[18-20]. There are, however, few studies on *APOOL* and *PLA2G6* in the growth and prognosis of tumors.

This study developed a nomogram for risk assessment based on multivariate Cox regression analysis to evaluate the OS of patients with esophageal cancer. The TNM stage and risk score are independent predictive factors for esophageal cancer, according to the univariate and multivariate Cox regression models. We further incorporated clinicopathological factors in addition to TNM stages and risk scores. The two histopathological types of primary esophageal cancer that are most frequently identified in clinics are squamous cell carcinoma and adenocarcinoma; they have the same potential risks, gene alterations, and treatments[21]. These two histopathological tumor types exhibit distinct behaviors in esophageal cancer, with squamous cell carcinoma exhibiting an earlier lymphatic migration and a poorer prognosis than adenocarcinoma[22]. Esophageal squamous cell carcinoma has a bad prognosis in



DOI: 10.12998/wjcc.v10.i33.12077 Copyright ©The Author(s) 2022.

Figure 2 Construction of a prognostic classifier based on platelet-associated genes. A and B: The results of the least absolute shrinkage and selection operator Cox regression suggest that four platelet-related genes were essential for the classifier; C: t-distributed stochastic neighbor embedding analysis; D: Principal component analysis plot. The expression levels of four biomarkers of the classifier in high- and low-risk group; E: Adenocarcinoma; F: Squamous cell carcinoma; G: All cases. t-SNE: t-distributed stochastic neighbor embedding.

terms of 5-year survival rates (15%–25%) since it is the most common subtype of esophageal cancer and has a higher occurrence in specific geographic areas[23]. The OS of esophageal cancer and the histopathological type were not significantly different in our study. But between the two pathological types, there was a statistically significant difference in the high-risk or low-risk groups. As a result, the nomogram also included pathological types.

In order to verify the nomogram’s effectiveness, its accuracy was assessed. The esophageal cancer cohort also demonstrated good calibration and discrimination; in particular, our high concordance index value (0.729) indicated the performance of the nomogram[24]. The nomogram had strong predictive power, as evidenced by the ROC curve, which had AUC values of 0.722 at 1 year, 0.831 at 2 years, and 0.843 at 3 years. The calibration curve’s observation and prediction exhibited a fair amount of agreement, indicating that the nomogram may be utilized to predict the 1-, 2-, and 3-year survival rates for the cohort with esophageal cancer[25]. Overall, the findings of the calibration curve, ROC curve, and concordance index revealed that our developed prediction nomogram had excellent prediction performance.

This study had a number of advantages. First, our study was the first to describe platelet-related genes and the prognosis of esophageal cancer. Four prognostic differential genes combined with histopathological types and TNM stages were used to construct a prognosis nomogram. The individualized prediction of this nomogram may reflect the survival rate of esophageal cancer candidates more correctly, making up for the inadequacy of earlier TNM stages. Second, our analysis differed from earlier research of similar studies. We choose more control group samples than in earlier research in order to exclude the interference of a small sample of the control group in the differential analysis. Finally, we developed a prognostic model that predicted 1-, 2-, and 3-year survival with high AUC utilizing a 4-gene signature, histopathological types, and TNM stages.

This study had a number of limitations. First, there was not enough esophageal cancer in our study’s sample to build prediction models based on adenocarcinoma and squamous cell carcinoma. Second, it was difficult to tell if the four DEGs differed between normal and malignant tissues due to a lack of additional histology specimens for external confirmation. Additionally, we utilized statistical analysis to find the related differential gene and GO and KEGG enrichment analysis to confirm the DEG’s pathway and enrichment function. There was no mechanism research to confirm these findings.

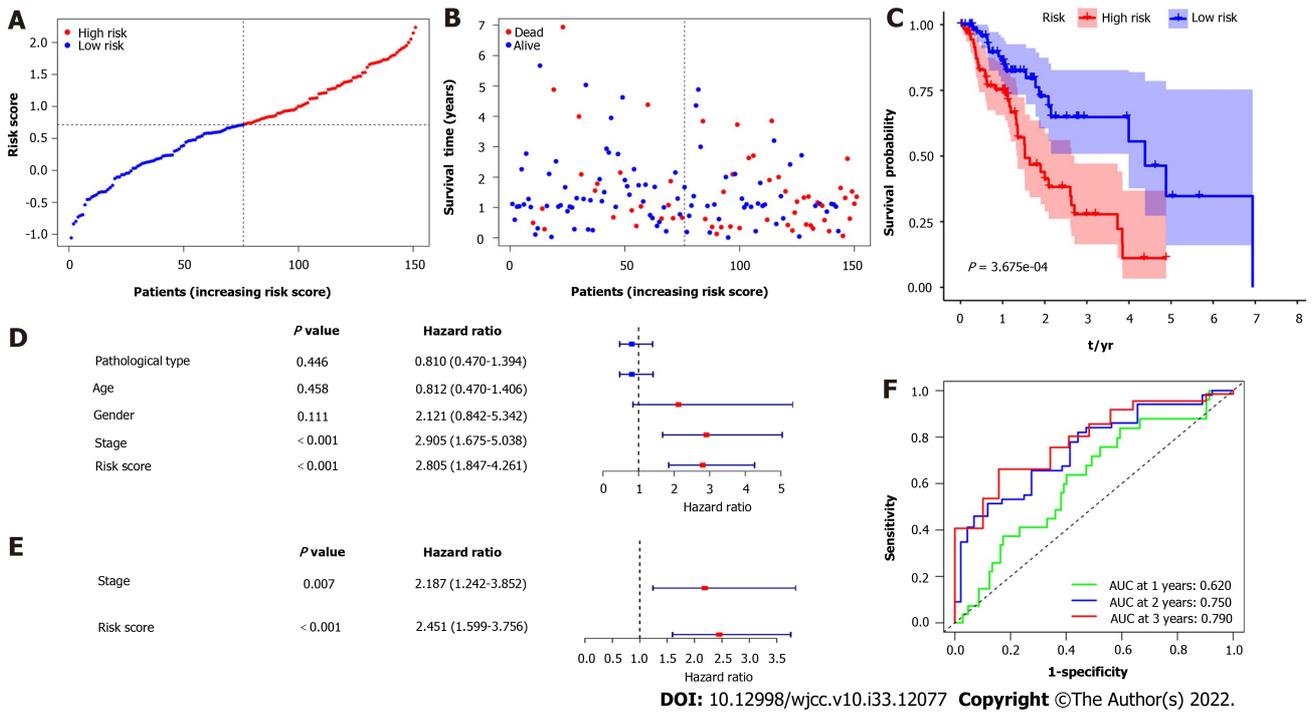


Figure 3 Prognostic analysis of the 4-gene signature model in the esophagus cancer cohort. A: Distribution and median value of the risk scores; B: Distributions of overall survival status, overall survival, and risk score; C: Kaplan-Meier curves for the overall survival of patients in the high-risk group and low-risk group; D and E: Univariate and multivariate Cox regression analyses regarding overall survival; F: Area under the curve of time-dependent receiver operating characteristic curves.

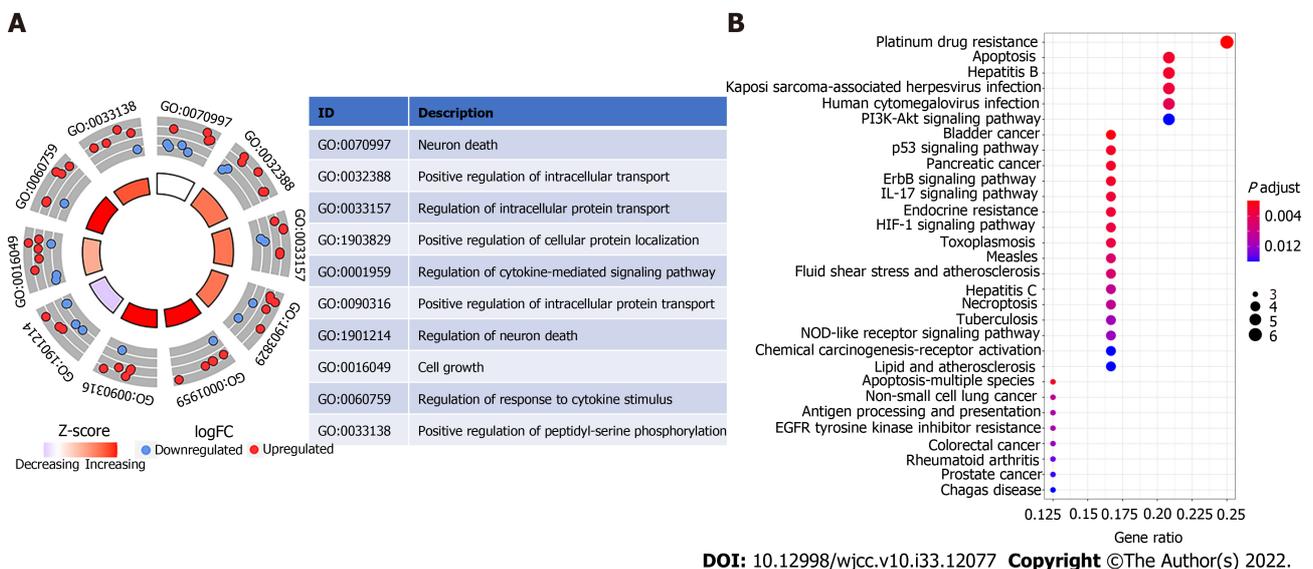


Figure 4 Representative results of Gene Ontology circle plot and Kyoto Encyclopedia of Genes and Genomes analyses. A: The inner ring is a bar plot where the height of the bar indicates the significance of the term (log10 adjusted P value), and color corresponded to the Z-score. The outer ring displays scatterplots of the expression levels (log fold change) for the genes in each term. The table represents the distribution of platelet-related genes in significant gene ontology terms; B: Most significant or shared Kyoto Encyclopedia of Genes and Genomes pathways. FC: Fold change; GO: Gene ontology.

CONCLUSION

In conclusion, we constructed a novel esophageal cancer risk model based on four platelet-related genes. It was a great prognostic information tool that could be utilized to supplement the TNM staging system combined with histopathological types and risk scores.

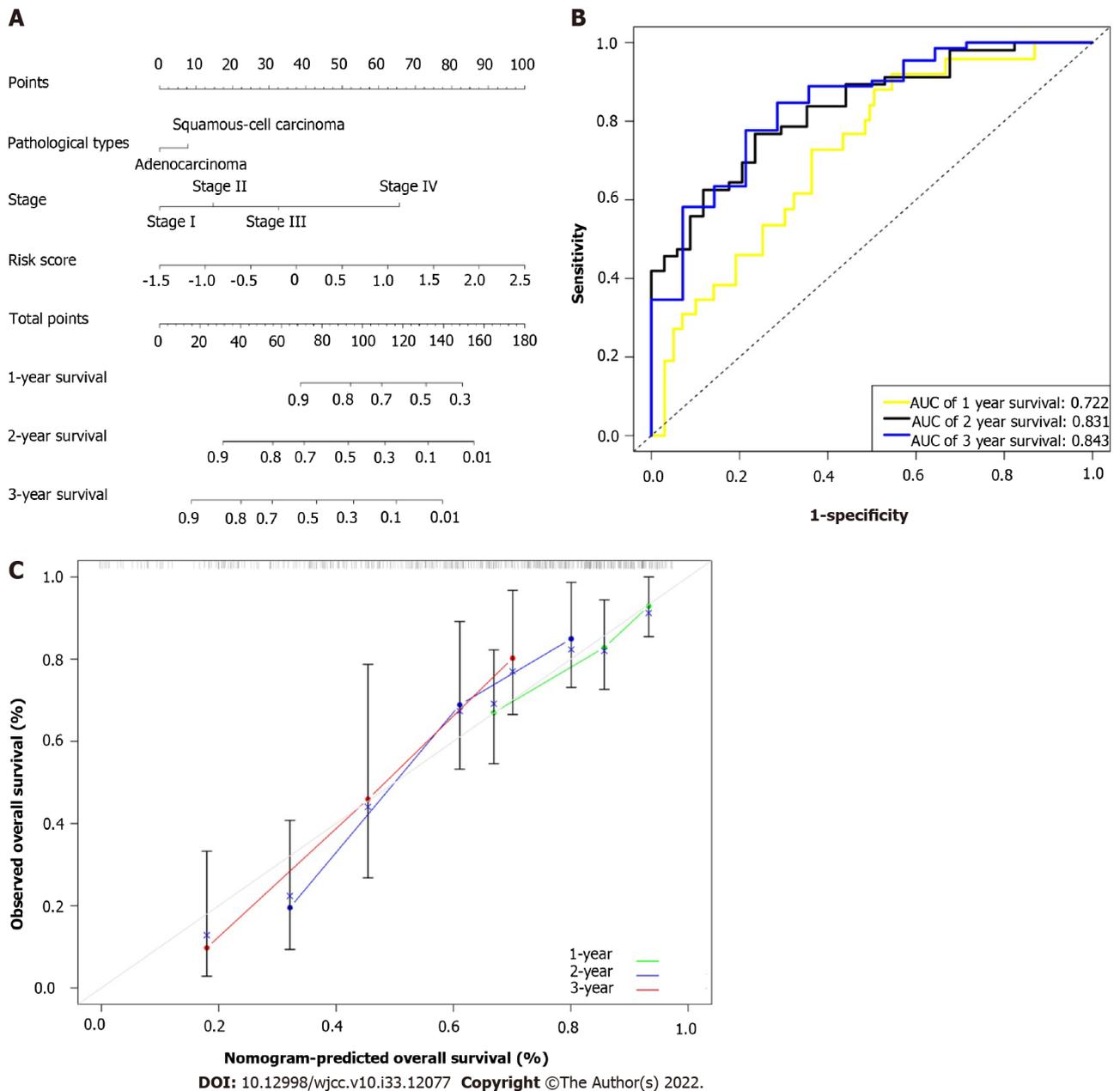


Figure 5 Construction of prognostic nomogram. A: Nomogram containing the risk score predicted the overall survival in patients with esophageal cancer; B: Receiver operating characteristic curves and area under the curve for 1-, 2-, and 3-year survival of the nomogram; C: Calibration curve of 1-, 2-, and 3-year survival in the nomogram and ideal model.

ARTICLE HIGHLIGHTS

Research background

The prognosis for esophageal cancer, one of the malignancies that responds least to cancer therapy, has not improved despite several breakthroughs in treatment. Improving patient outcomes depends on finding biomarkers and comprehending the molecular causes of esophageal cancer.

Research motivation

We wanted to create a risk score based on platelet-related gene signatures for prognosis prediction since the expression of platelet-related genes is strongly linked to patient prognosis.

Research objectives

To predict esophageal cancer prognosis, a risk model and nomogram constructed based on platelet-related gene signatures and clinical factors associated with prognosis could be utilized.

Research methods

We constructed a trustworthy platelet-related gene signature to predict the prognosis of esophageal cancer using 151 samples of the disease. Then, an integrated nomogram for clinical practice was created utilizing a combined risk score, risk score, and TNM stage. The prognostic accuracy of the model was also supported by the receiver operating characteristic curve, concordance index, and related calibration curve.

Research results

The survival curve was created after constructing a prognostic risk model based on four platelet genes associated with prognosis. Patients in the high-risk group had a considerably lower life expectancy than those in the low-risk group, according to the Kaplan-Meier survival analysis. The risk score was an independent factor in predicting survival, according to results from both univariate and multivariate Cox regression analyses.

Research conclusions

We identified a four-gene signature, constructed a risk score, and developed a prediction nomogram for patients with esophageal cancer based on the risk score, TNM staging, and histopathological type.

Research perspectives

Identification and prediction of prognostic indicators are essential for esophageal cancer patients.

FOOTNOTES

Author contributions: Du QC and Wang XY analyzed the data and wrote the manuscript, and both have contributed equally to this work; Yu H designed the study; Hu CK, Zhou L, Fu Z, Liu S, Wang J, Ma YY, and Liu MY collected the data and revised the paper; all authors have read and approved the final manuscript.

Institutional review board statement: The data for the study came from public databases and did not involve blood or tissue samples from humans or animals. Therefore, there were no ethical issues involved in this study.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Qian-Cheng Du 0000-0002-0154-2210; Xin-Yu Wang 0000-0001-8488-7910; Cheng-Kai Hu 0000-0002-7670-5707; Ling Zhou 0000-0003-2290-3756; Zheng Fu 0000-0002-6373-4998; Shun Liu 0000-0001-7607-1567; Jian Wang 0000-0002-7244-4976; Ying-Ying Ma 0000-0003-3015-9242; Meng-Yao Liu 0000-0002-4211-0748; Hua Yu 0000-0002-1599-6192.

S-Editor: Xing YX

L-Editor: Filipodia

P-Editor: Xing YX

REFERENCES

- 1 **Yan MH**, Hou XB, Cai BN, Qu BL, Dai XK, Liu F. Neoadjuvant chemoradiotherapy plus surgery in the treatment of potentially resectable thoracic esophageal squamous cell carcinoma. *World J Clin Cases* 2020; **8**: 6315-6321 [PMID: 33392312 DOI: 10.12998/wjcc.v8.i24.6315]
- 2 **Lv J**, Guo L, Liu JJ, Zhao HP, Zhang J, Wang JH. Alteration of the esophageal microbiota in Barrett's esophagus and esophageal adenocarcinoma. *World J Gastroenterol* 2019; **25**: 2149-2161 [PMID: 31143067 DOI: 10.3748/wjg.v25.i18.2149]
- 3 **Wang YQ**, Zhi QJ, Wang XY, Yue DS, Li K, Jiang RC. Prognostic value of combined platelet, fibrinogen, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with lung adenocarcinoma. *Oncol Lett* 2017; **14**: 4331-4338 [PMID: 28943947 DOI: 10.3892/ol.2017.6660]
- 4 **Li F**, Wang L, Zhang Y, Feng W, Ju T, Liu Z, Wang Z, Du X. A Retrospective Study on Using a Novel Single Needle Cone Puncture Approach for the Iodine-125 Seed Brachytherapy in Treating Patients With Thoracic Malignancy. *Front Oncol* 2021; **11**: 640131 [PMID: 34136382 DOI: 10.3389/fonc.2021.640131]
- 5 **Han D**, Zhang J, Zhao J, Lei T, Chen X, Zhang T, Wei H, Guan Y, Wang J, Zhang W, Zhao L, Yuan Z, Song Y, Liu N,

- Pang Q, Wang P. Platelet-to-lymphocyte ratio is an independent predictor of chemoradiotherapy-related esophageal fistula in esophageal cancer patients. *Ann Transl Med* 2020; **8**: 1163 [PMID: 33241012 DOI: 10.21037/atm-20-4053]
- 6 **Zhang T**, Nie Y, Xia H, Zhang Y, Cai K, Chen X, Li H, Wang J. Identification of Immune-Related Prognostic Genes and LncRNAs Biomarkers Associated With Osteosarcoma Microenvironment. *Front Oncol* 2020; **10**: 1109 [PMID: 32793475 DOI: 10.3389/fonc.2020.01109]
 - 7 **Cui MT**, Liang ZW, Sun YZ, Wu J, Lu H, Wang WJ, Xu MD, Jiang M, Li W, Qian J, Duan WM. The prognostic roles of red blood cell-associated indicators in patients with resectable gastric cancers. *Transl Cancer Res* 2020; **9**: 2300-2311 [PMID: 35117591 DOI: 10.21037/tcr.2020.03.46]
 - 8 **Baba Y**, Nomoto D, Okadome K, Ishimoto T, Iwatsuki M, Miyamoto Y, Yoshida N, Baba H. Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma. *Cancer Sci* 2020; **111**: 3132-3141 [PMID: 32579769 DOI: 10.1111/cas.14541]
 - 9 **Xu S**, Zhou Y, Biekemitoufu H, Wang H, Li C, Zhang W, Ma Y. Expression of Twist, Slug and Snail in esophageal squamous cell carcinoma and their prognostic significance. *Oncol Lett* 2021; **21**: 184 [PMID: 33574923 DOI: 10.3892/ol.2021.12445]
 - 10 **Kuwai T**, Yamaguchi T, Imagawa H, Miura R, Sumida Y, Takasago T, Miyasako Y, Nishimura T, Iio S, Yamaguchi A, Kouno H, Kohno H, Ishaq S. Endoscopic submucosal dissection for early esophageal neoplasms using the stag beetle knife. *World J Gastroenterol* 2018; **24**: 1632-1640 [PMID: 29686470 DOI: 10.3748/wjg.v24.i15.1632]
 - 11 **Hirahara N**, Tajima Y, Fujii Y, Kaji S, Yamamoto T, Hyakudomi R, Taniura T, Kawabata Y. Comprehensive Analysis of Red Blood Cell Distribution Width as a Preoperative Prognostic Predictor in Gastric Cancer. *Anticancer Res* 2019; **39**: 3121-3130 [PMID: 31177157 DOI: 10.21873/anticancerres.13448]
 - 12 **Huh G**, Ryu JK, Chun JW, Kim JS, Park N, Cho IR, Paik WH, Lee SH, Kim YT. High platelet-to-lymphocyte ratio is associated with poor prognosis in patients with unresectable intrahepatic cholangiocarcinoma receiving gemcitabine plus cisplatin. *BMC Cancer* 2020; **20**: 907 [PMID: 32967632 DOI: 10.1186/s12885-020-07390-3]
 - 13 **Yang J**, Xu H, Guo X, Zhang J, Ye X, Yang Y, Ma X. Pretreatment Inflammatory Indexes as Prognostic Predictors for Survival in Colorectal Cancer Patients Receiving Neoadjuvant Chemoradiotherapy. *Sci Rep* 2018; **8**: 3044 [PMID: 29445100 DOI: 10.1038/s41598-018-21093-7]
 - 14 **Bang KH**, Na YG, Huh HW, Hwang SJ, Kim MS, Kim M, Lee HK, Cho CW. The Delivery Strategy of Paclitaxel Nanostructured Lipid Carrier Coated with Platelet Membrane. *Cancers (Basel)* 2019; **11**: 807 [PMID: 31212681 DOI: 10.3390/cancers11060807]
 - 15 **Chen L**, Zeng H, Yang J, Lu Y, Zhang D, Wang J, Kuang C, Zhu S, Wang M, Ma X. Survival and prognostic analysis of preoperative inflammatory markers in patients undergoing surgical resection for laryngeal squamous cell carcinoma. *BMC Cancer* 2018; **18**: 816 [PMID: 30103707 DOI: 10.1186/s12885-018-4730-x]
 - 16 **Zhu L**, Dong L, Feng M, Yang F, Jiang W, Huang Z, Liu F, Wang L, Wang G, Li Q. Profiles of autophagy-related genes in esophageal adenocarcinoma. *BMC Cancer* 2020; **20**: 943 [PMID: 32998713 DOI: 10.1186/s12885-020-07416-w]
 - 17 **Bi Y**, Kong P, Zhang L, Cui H, Xu X, Chang F, Yan T, Li J, Cheng C, Song B, Niu X, Liu X, Xu E, Hu X, Qian Y, Wang F, Li H, Ma Y, Yang J, Liu Y, Zhai Y, Wang Y, Zhang Y, Liu H, Liu J, Wang J, Cui Y, Cheng X. EP300 as an oncogene correlates with poor prognosis in esophageal squamous carcinoma. *J Cancer* 2019; **10**: 5413-5426 [PMID: 31632486 DOI: 10.7150/jca.34261]
 - 18 **Alsamri H**, Hasasna HE, Baby B, Alneyadi A, Dhaheri YA, Ayoub MA, Eid AH, Vijayan R, Iratni R. Carnosol Is a Novel Inhibitor of p300 Acetyltransferase in Breast Cancer. *Front Oncol* 2021; **11**: 664403 [PMID: 34055630 DOI: 10.3389/fonc.2021.664403]
 - 19 **Li J**, Huang C, Xiong T, Zhuang C, Li Y, Ye J, Gui Y. A CRISPR Interference of CBP and p300 Selectively Induced Synthetic Lethality in Bladder Cancer Cells *In Vitro*. *Int J Biol Sci* 2019; **15**: 1276-1286 [PMID: 31223286 DOI: 10.7150/ijbs.32332]
 - 20 **Du C**, Huang D, Peng Y, Yao Y, Zhao Y, Yang Y, Wang H, Cao L, Zhu WG, Gu J. 5-Fluorouracil targets histone acetyltransferases p300/CBP in the treatment of colorectal cancer. *Cancer Lett* 2017; **400**: 183-193 [PMID: 28465257 DOI: 10.1016/j.canlet.2017.04.033]
 - 21 **Okuda Y**, Shimura T, Iwasaki H, Fukusada S, Nishigaki R, Kitagawa M, Katano T, Okamoto Y, Yamada T, Horike SI, Kataoka H. Urinary microRNA biomarkers for detecting the presence of esophageal cancer. *Sci Rep* 2021; **11**: 8508 [PMID: 33879806 DOI: 10.1038/s41598-021-87925-1]
 - 22 **Liu CC**, Chou KT, Hsu JW, Lin JH, Hsu TW, Yen DH, Hung SC, Hsu HS. High metabolic rate and stem cell characteristics of esophageal cancer stem-like cells depend on the Hsp27-AKT-HK2 pathway. *Int J Cancer* 2019; **145**: 2144-2156 [PMID: 30920655 DOI: 10.1002/ijc.32301]
 - 23 **Wang X**, Kutschat AP, Yamada M, Prokakis E, Böttcher P, Tanaka K, Doki Y, Hamdan FH, Johnsen SA. Bromodomain protein BRDT directs Δ Np63 function and super-enhancer activity in a subset of esophageal squamous cell carcinomas. *Cell Death Differ* 2021; **28**: 2207-2220 [PMID: 33658703 DOI: 10.1038/s41418-021-00751-w]
 - 24 **Liu H**, Zhang Z, Huang Y, Wei W, Ning S, Li J, Liang X, Liu K, Zhang L. Plasma HSP90AA1 Predicts the Risk of Breast Cancer Onset and Distant Metastasis. *Front Cell Dev Biol* 2021; **9**: 639596 [PMID: 34109171 DOI: 10.3389/fcell.2021.639596]
 - 25 **Lindhiem O**, Petersen IT, Mentch LK, Youngstrom EA. The Importance of Calibration in Clinical Psychology. *Assessment* 2020; **27**: 840-854 [PMID: 29457474 DOI: 10.1177/1073191117752055]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

