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Prognostic Value of Immune-Related Genes in Esophageal Adenocarcinoma

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ABSTRACT Esophageal adenocarcinoma (EAC) is among the most aggressive and lethal malignancies in gastrointestinal tumours. Recently, immunotherapy has gained prominence, highlighting the need for systematic exploration of immune-related genes (IRGs) in EAC to advance treatment and prognostication. Differential gene expression profiles from EAC and adjacent tissues were retrieved through applying the TCGA database. Cross-referencing with immune gene lists from TCGA and GEO (GSE19417) was to identify differentially expressed IRGs (DEIRGs). The researchers established a prognostic mode via employing lasso-penalised Cox regression and this model was validated using GSE19417, which also assessed six tumour-infiltrating immune cell subtypes. A total of 259 DEIRGs were identified, with 10 significantly correlating with overall survival (OS) in EAC. Functional enrichment analysis revealed involvement in extracellular region and cytokine-cytokine receptor interaction. High-risk scores and the AJCC stage were found to be independently linked with worse OS. The study underscores the prognostic relevance of IRGs, informing future EAC prognosis and immunotherapy strategies.

INTRODUCTION

Esophageal cancer (EC), constituted of esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), ranks one of malignant tumours featured with high aggression and mortality in gastrointestinal tract tumours (Zhang et al. 2024). ESCC accounts for about 90 percent of such cases in the world, but the incidence of EAC is on the rise (Strzelec et al. 2024). Compared with ESCC, EAC has a worse prognosis (Ge et al. 2024). Despite improvements in treatment in the last decade, the 5-year survival rate takes proportion of less than 25 percent for EAC patients yet, and 20 percent of them were IV stage in the diagnosis (Tramontano et al. 2017). As a result, it is of necessity to explore new prognostic markers and new adjuvant therapy for EAC.

As it is known, the immunity of tumours is of great significance during occurring, developing, migrating and even harvesting drug resistance in tumours (Giraldo et al. 2014). Tumour escape from the immune system involves the reduction of tumour antigen recognition by immune cells and immunosuppressive microenvironment development (Koti et al. 2015; Pietras and Ostman 2010). Therefore, exploiting the immune system to positively combat cancer is an important direction of research. In recent years, immunotherapy has been an emerging field (Carter et al. 2017; Li et al. 2015). PD-L1/PD-1 immune checkpoint has been revealed to function in many solid tumours, such as hepatocellular carcinoma (Li et al. 2015), lung squamous cell carcinoma (Carter et al. 2017), as well as renal cell carcinoma (Motzer et al. 2016). However, the immunity-related molecular mechanism on EAC has not been systematically studied. Immune-related genes (IRGs) have been clarified as promising indicators

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for prognosis in tumour progression (Choi et al. 2014; Fehlker et al. 2014). There are no investigations on the prognostic significance of IRGs in EAC.

Objective

In order to inquiry the prognostic significance of IRGs in EAC and and rediscover their clinical application values, the researchers integrated and compared IRGs expressions between EAC and adjacent normal tissues, and obtained significant differential IRGs. A prognostic model was then established to comprehensively explore the prognostic value of the IRGs in EAC. $CD8^+$ T cell infiltration was observed to be involved in the prognostic model. It is expected to provide direction for good prognosis and personalised treatment in EAC patients.

MATERIAL AND METHODS

Acquiring and Processing Data

For EAC patients, TCGA data portal (origin of website: https://tcga-data.nci.nih.gov/tcga/) along with GEO database (GSE19417) were to harvest Transcriptome RNA-sequencing data and clinical data. In total, 78 EAC tissues and 9 normal paired tissues were enrolled in TCGA, 49 EAC tissues were included in GSE19417. Through previous work (Bhattacharya et al. 2014), the database of Immunology Database and Analysis Portal (ImmPort) was applied to download the list of IRGs.

Identification of Differentially Expressed Genes, Differentially Expressed Immune-related Genes and Survival-Associated Immune-related Genes

Through the edgeR package in the R language that was obtained from the website of http://bioconductor.org/packages/edgeR/, the differentially expressed genes (DEGs) were identified. According to the Macklaim's work (Macklaim et al. 2013), the thresholds followed a |log2 fold change (FC)| > 1.0 and false discovery rate (FDR) adjusted to $P < 0.05$. Subsequently, gplots and heatmap packages were to produce volcano, heat maps of the DEGs in the edgeR package. The differentially expressed IRGs (DEIRGs) were discovered through weighing with IRGs lists witnessed in both the TCGA database and GSE19417. And univariate COX analysis could be applied to identify survival-associated IRGs.

The Operation of Functional Enrichment Analysis

By tool of Database for annotation, visualisation, and integrated discovery (DAVID, https://david.ncifcrf.gov/) (Slemc and Kunej 2016) and cluster profiler that represented R package to conduct functional classification and enrichment in gene clusters, Gene Ontology (GO) as well as Kyoto Encyclopedia of Genes and Genomes (KEGG), based on the threshold of $P < 0.05$, were used to study biological mechanisms of the IRGs. The overall analysis results were presented in the GO plot package by approach of R software.

Development and Validation of the Prognostic Model Aimed at IRGs

Through multivariate, lasso penalised COX measurements, R software survival package was employed to choose the survival-associated IRGs. Then, high-risk group and low-risk group were separated on account of the standard of median risk score value, which was calculated by the formula of the total of The PGF level * (0.13173), The IL1B level * (0.02123) and The GDF-15 level* (0.00730). And the feasibility of the IRG Prognostic Model (IRGPM) was confirmed through dividing GSE19417 patients into two groups on the basis of assessing the median risk score. The survival situation in distinct groups was adjusted by the Kaplan-Meier (KM) curve.

The Associated Measurement of Between IRGPM, Genes and Immune Cells Infiltration

For tumour infiltrating immune cells including CD4+ T cells, CD8+T cells, B cells, macrophages, dendritic cells and neutrophils, the abundances were analysed and visualised with the assistance of the online database-Tumor Immune Estimation Resource (TIMER, http://timer.comp-genomics.org/timer/) (Zeelen et al. 2017). And the researchers took the relationship between immune cells infiltration and other parameters into observation. The researchers downloaded and analyzed immune infiltrate levels, then to evaluate their correlations with the IRGPM, genes in EAC patients .

The Performing of Quantitative Real-time PCR (qRT-PCR)

In 15 samples from EAC patients, total RNA was obtained, reversely transcribed respectively

by using Invitrogen's TRIzol reagent (Carlsbad, USA), the New England Biolabs's First Strand cDNA synthesis kit offered from Beijing (China). SYBR Green PCR kit obtained from Applied Biological Materials in Richmond (Canada) was to operate amplifications on Applied Biosystems's 7500 Real-Time PCR System provided by Foster city in USA. Finally, RNA expression was normalised via utilizing the $2^{-\Delta\Delta Ct}$ method, which was against GAPDH. The PCR primers used in this research were exhibited in Table 1. Three separate experiments in every sample were done.

Statistical Analysis

The professional analysis of the data were taken on conduction using the version 8.0 of GraphPad Prism (San Diego, USA). By means of the "survival" package in R, the researchers performed survival analysis for EAC patients in a prognostic model. The KM method combined with the log-rank test were to make survival curves. Survival receiver operating characteristic (ROC) R software package (Zheng et al. 2006) was employed to figure out area under the curve (AUC). And Spearman's rank correlation analysis was applied to take the link between risk grade, genes distribution and immune cells infiltration into assessment. $P < 0.05$ was regarded as the phenomenon that there was statistically significant variance.

RESULTS

Identification of DEGs, DEIRGs in EAC

In summary, 3,643 DEGs in EAC were discovered, with 3,017 genes being upregulated and 626 genes downregulated in EAC compared to normal esophageal tissues (Fig. 1A, B). The heatmap (Fig. 1A) clearly illustrates the distinct expression patterns between EAC and normal tissues, while the volcano plot (Fig. 1B) highlights the significant upregulation and downregulation of these genes. This extensive set of DEGs provides a broad foundation for understanding the molecular mechanisms underlying EAC.

From this set of DEGs, the researchers further identified 259 DEIRGs by cross-referencing with the TCGA immune gene list. Among these DEIRGs, 226 were upregulated and 33 were downregulated (Fig. 1C, D). The distinct pattern of the expression of IRGs was evident in the heatmap (Fig. 1C), and the volcano plot (Fig. 1D) visually emphasized the significant immune-related changes in EAC, suggesting that dys-regulated immunity could exert a crucial role in the pathogenesis of this cancer.

Identification of Survival-associated IRGs

Through intersection analysis of the TCGA database and the GSE19417 dataset, the researchers identified 10 IRGs (IL1B, FABP2, GDF15, MAPT, PGF, TNFSF18, IL17RB, RORC, HSPA6, and HSP90AA1) that were notably involved in the relationship with overall survival (OS) in EAC patients (Table 2). These genes were not just markers but were actively involved in survival outcomes, making them potential targets for therapeutic intervention.

Gene Functional Enrichment Analysis of DEIRGs

To delve into the biological significance of the 259 DEIRGs, the researchers performed GO and KEGG pathway analyses. It was revealed that these DEIRGs were mainly enriched in the extracellular region, extracellular region part, extracellular space, and

Table 1: Primer sequences for RT-PCR

Primer	*Seqence 5'-3'*
PGF forward	CTGCGAATGCCGGCCTCT
PGF reverse	GCACCTTTCCGGCTTCAT
IL-1B forward	TGGCAGAAAGGGAACAGAAAGG
IL-1B reverse	AACAAAAGGGCTGGGGATTGG
GDF15 forward	CAATCCCATGGTGCTCATTC
GDF15 reverse	TATGCAGTGGCAGTCTTTGG
GAPDH forward	CAACGAATTTGGCTACAGCA
GAPDH reverse	AGGGGTCTACATGGCAACTG

Abbreviations: RT-PCR Quantitative real-time PCR

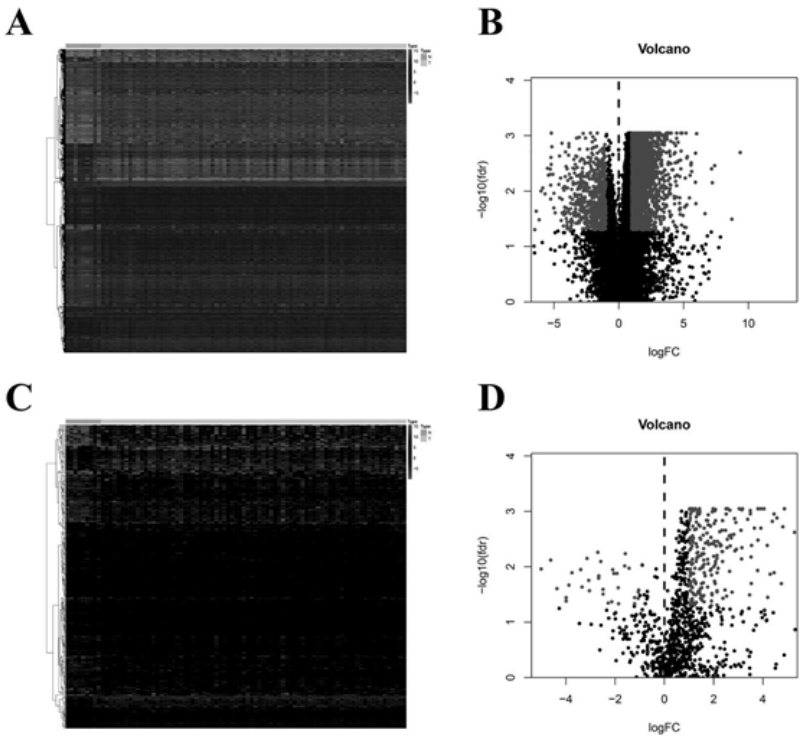

Fig. 1. Heatmaps along with Volcano plots of Differentially expressed genes (DEGs, A-B), differentially expressed immune-related genes (DEIRGs, C-D) between EAC tissues and normal esophageal tissues. The red point (up-regulated genes with statistical significance), the green point (downregulated genes with statistical significance)

Table 2: Univariate Cox regression analysis between IRGS and Overall Survival

Risk factors	*Overall Survival (OS)*	
	HR (95% CI)	*P value*
IL1B	1.218 (1.578-1.818)	0.002
FABP2	1.343 (1.659-2.106)	0.025
GDF15	1.345 (1.188-1.951)	0.003
MAPT	1.665 (1.322-2.098)	0.029
PGF	1.628 (1.249-2.236)	<0.001
TNFSF18	1.126 (1.072-1.665)	0.014
IL17RB	1.178 (1.093-1.802)	0.017
RORC	0.811 (0.753-0.912)	0.034
HSPA6	1.178 (1.233-1.672)	0.024
HSP90AA1	1.151 (1.063-1.632)	0.031

Abbreviations: CI confidence interval, HR hazard ratio

immune response (Fig. 2A, B). The top 10 frequent GO networks (Fig. 2B) further highlight the predominant biological processes these genes are involved in, particularly in immune-related activities, which are critical in tumour-immune interactions.

In the KEGG analysis, the top 10 enriched pathways, composing of cytokine-cytokine receptor interaction, chemokine signalling pathway, IL-17 signalling pathway, MAPK signalling pathway, PI3K-Akt signalling pathway, Rap1 signalling pathway, viral protein interaction with cytokine and cytokine receptor, were discovered (Fig. 3B). These pathways are crucial for immune modulation and cancer progression, suggesting that these DEIRGs could be involved in the complex network of tumour-immune system interactions. A visual network of these relationships using Cytoscape v3.6.1 illustrated the intricate connections between the IRGs and the KEGG pathways that were involved in prognosis (Fig. 3A).

The Efficacy of Prognostic Model

Using univariate analysis, the researchers identified key survival-associated genes (Table 2), which were further refined to build a prognostic

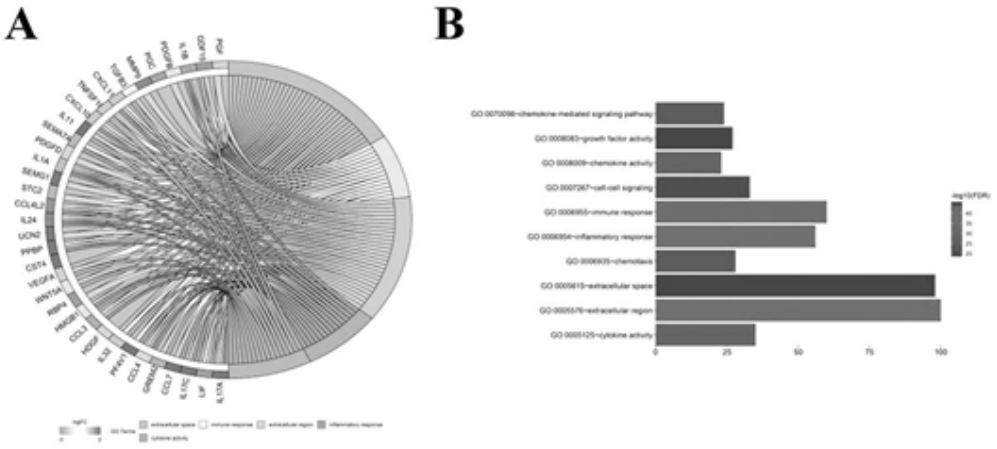

Fig. 2. The enriched GO biological process terms of DEIRGs
Pie chart for the enriched top 10 frequent GO networks of DEIRGs (Fig. 2A). Histogram for the enriched top 10 frequent GO networks of DEIRGs (Fig. 2B)

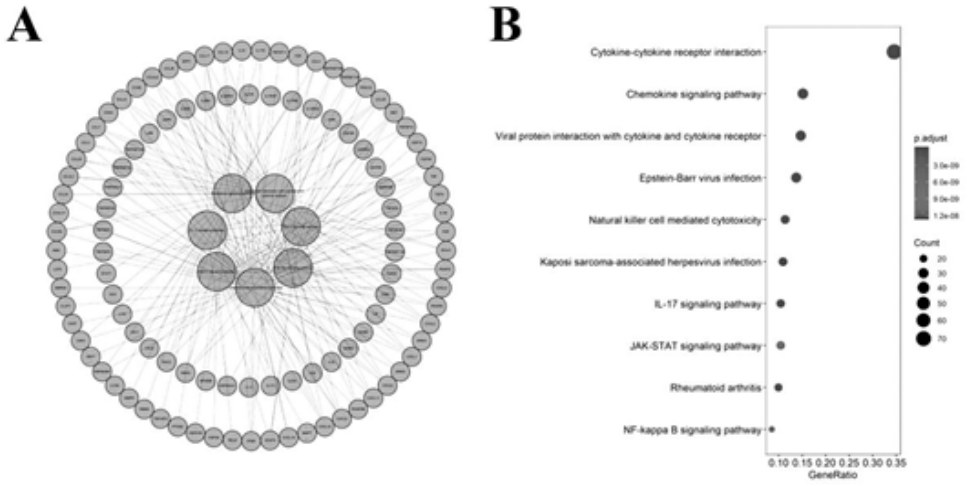

Fig. 3. The enriched KEGG pathways and the intersection network
The network between the IRGs and prognostic involved KEGG pathways was visualized in Fig. 3A. Top 10 enriched KEGG pathways of DEIRGs were exhibited in Fig. 3B.

model (Fig. 4). The model's robustness was validated using the GSE19417 datase in which patients were stratified into high-risk and low-risk groups. The heatmap in Figure 4A represented the expression profiles of the vital prognostic IRGs, while risk scores along with survival status were presented in Figure 4B and 4C, respectively. This model effectively stratified patients into distinct prognostic categories, which could be crucial for personalised treatment strategies.

Survival of Prognostic Model in EAC Patients

The KM survival analysis in Figure 5A noted that there was a statistical variance in OS among two groups with high-risk and low-risk in the TCGA

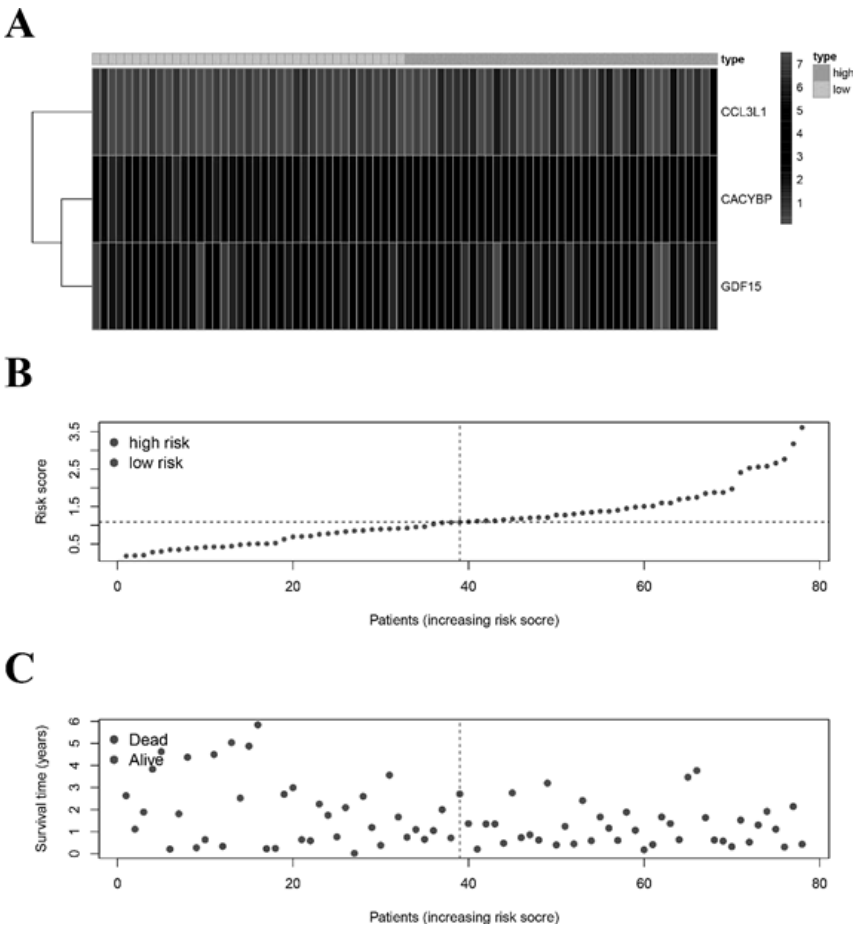

Fig. 4. The prognostic model of IRGs was established and assessed.
Fig. 4A showed Heatmap of the included IRGs expression profiles. Fig. 4B showed Rank of prognostic index and distribution of high-risk, low-risk groups. Fig. 4C showed Survival status of suffers in groups with different risks

prognostic model (P < 0.001). Univariate analysis in Figure 5B demonstrated that high AJCC stage with HR of 4.082 and 95 % CI of 1.700-9.803, high N stage with HR of 3.931 and 95 % CI of 1.317-11.396, and high-risk score with HR of 4.241 and 95 % CI of 1.756-10.243, were significant to provide prognosis reference for OS in EAC patients, with P of 0.002, 0.014, 0.001 separately. Furthermore, high AJCC stage (HR: 4.513; 95% CI: 1.082-9.321) together with high-risk score (HR: 4.137; 95% CI: 1.454-9.722) independently correlated with worse OS, with P of 0.039, 0.008 separately (Fig. 5C).

In the GSE19417, the survival analysis in Figure S2A was also variable between two groups (P=0.004). Univariate and multivariate analyses in this cohort further supported the self-contained prognostic efficacy of the risk score and N stage for OS (Fig. S2B, S2C).

Clinical Outcome of TCGA Prognostic Model in EAC Patients

It was found that the risk score evidently correlated with the AJCC stage in Figure 6A (P=0.014),

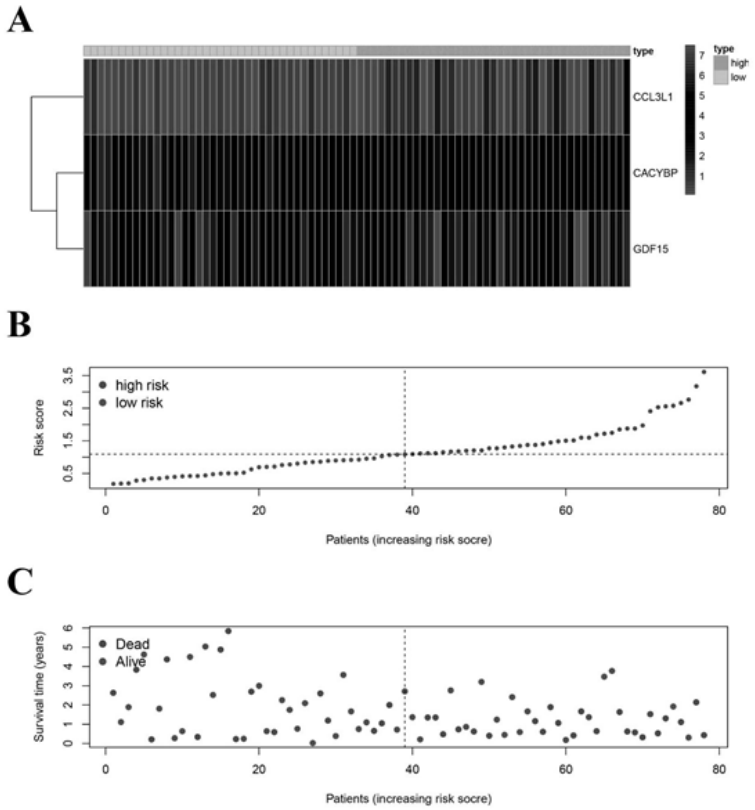

Fig. S1. Construct prognostic model of GSE19417 in EAC
Fig. S1A showed Heatmap of the included IRGs expression profiles. Fig. S1B showed Rank of prognostic index and distribution of high-risk, low-risk groups

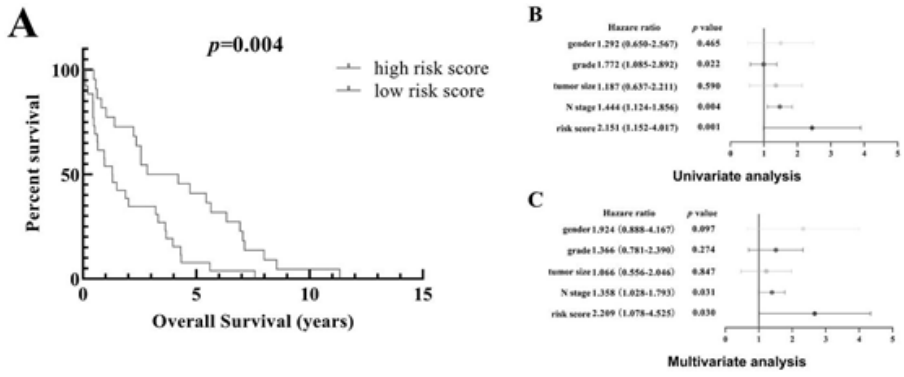

Fig. S2. The survival analysis of GSE19417 prognostic model in EAC
Patients in high risk group suffered shorter survival probability (Fig. S2A). Univariate Cox regression analysis of EAC (Fig. S2B). Multivariate Cox regression analysis of EAC (Fig. S2C)

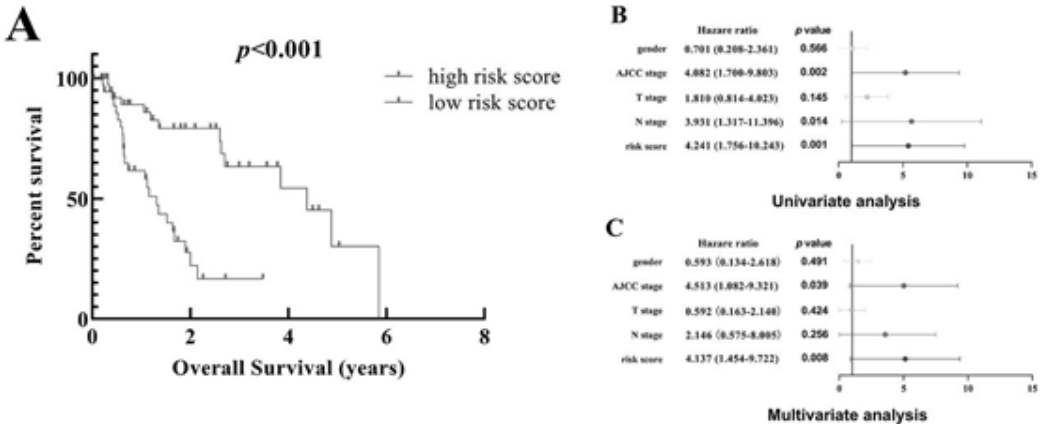

Fig. 5. The survival analysis of TCGA prognostic model in EAC
KM curve indicated high risk group experienced shorter survival probability (Fig. 5A). Univariate Cox regression analysis of EAC (Fig. 5B). Multivariate Cox regression analysis of EAC (Fig. 5C)

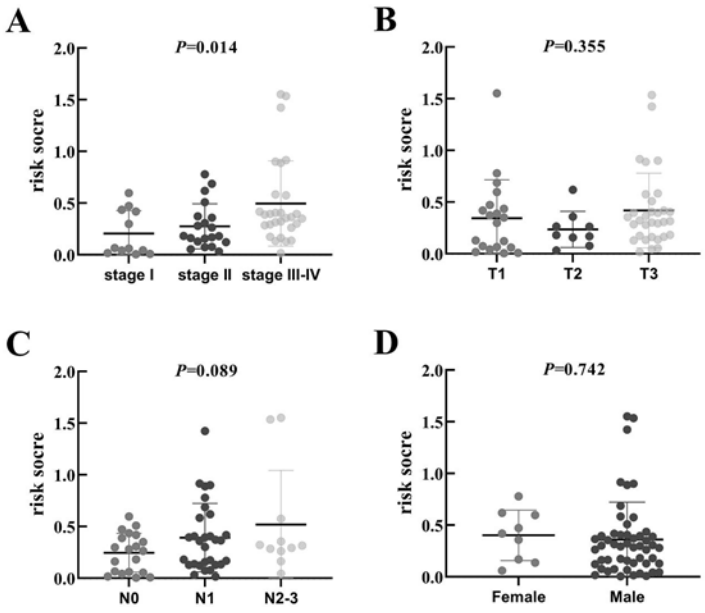

Fig. 6. The clinical outcome of TCGA prognostic model in EAC patients
The relationships between risk score and AJCC stage (Fig. 6A), T stage (Fig. 6B), N stage (Fig. 6C) and gender (Fig. 6D) of EAC patients

indicating that the model could reflect tumour progression. However, no significant associations were observed between risk score and T stage, N stage, or gender (Fig. 6B-D), suggesting that the model's predictive power is independent of these factors.

Verifying the Accuracy of Models

The TCGA model achieved an AUC of 0.724 and C-index of 0.741 (Fig. 7A, B), indicating good predictive accuracy. Similarly, the GSE19417 vali-

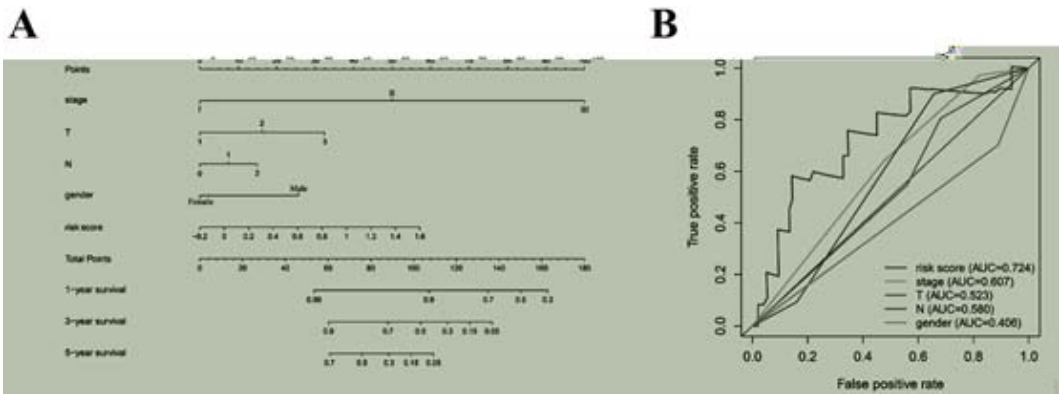

Fig. 7. The ROC curve and nomogram of TCGA prognostic model in EAC
The nomogram of TCGA model (Fig. 7A). The ROC curve of TCGA model (Fig. 7B)

dation model showed an AUC of 0.700 and a C-index of 0.723 (Fig. S3A, B), further validating the model's robustness.

Prognostic Model, Genes Expression, Immune Cell Infiltration Correlation Analysis

The investigators employed TCGA data to find out the possible relationship between the risk score and B cells, CD4+ T cells, CD8+ T cells, dendritic cells, macrophages, neutrophils and noticed that there was a significantly negatively associated effect between the risk score and CD8+ T cell infiltration, accompanied with Cor of -0.255 (P=0.024, Fig. 8A), suggesting a possible mechanism of immune evasion in high-risk patients. Additionally, in Figure 9A-E, S4A-M, PGF expression was proved to be positively linked with CD4+ T cells with Cor of 0.234 (P=0.039), macrophages with Cor of 0.311 (P=0.006), dendritic cells with Cor of 0.438 (P<0.001), and neutrophils with Cor of 0.234 (P=0.039). Conversely, GDF-15 expression had a negative correlation with neutrophils with Cor of -0.215 (P=0.049), highlighting the complicated interplay when considering tumour biology and immune cell infiltration.

The Analysis and Validation of PGF, IL1B, GDF-15 Expression in EAC

The expression patterns of PGF, IL1B, and GDF-15 were consistent with those observed in the TCGA database that was shown in Figure 10A-C. This consistency reinforces the reliability of the findings and supports the relevance of these genes in EAC progression.

DISCUSSION

At present, esophageal cancer characterized with the sixth predominant contributor of tumor-associated death still represents a significant global problem (Cheng et al. 2024). The treatment of EAC has progressed slowly and the clinical outcomes in the advanced stage are disappointing (Mansour et al. 2017; Walsh et al. 1996). IRGs are discovered to exert promising effect as prognostic indicators in tumour progression and immunotherapeutics (Choi et al. 2014; Wu et al. 2018). However, there is no comprehensive genetic analysis in EAC to explore its molecular mechanism. In this paper, the researchers intend to use IRGs to help predict the prognosis outcome of EAC suffers, helping understand the clinical significance and molecular characteristics.

By making the TCGA database with all immune genes compared, the researchers identified the DEIRGs. Based on further survival and clinical analysis, 10 vital DEIRGs (IL1B, FABP2, GDF15, MAPT, PGF, TNFSF18, IL17RB, RORC, HSPA6 and HSP90AA1) associated with prognosis were gained.

To detailedly explore the prognostic significance of IRGs in EAC, the researchers explored individualised characteristics linked with immunity to benefit the prognosis of patients. The researchers found that several important IRGs can

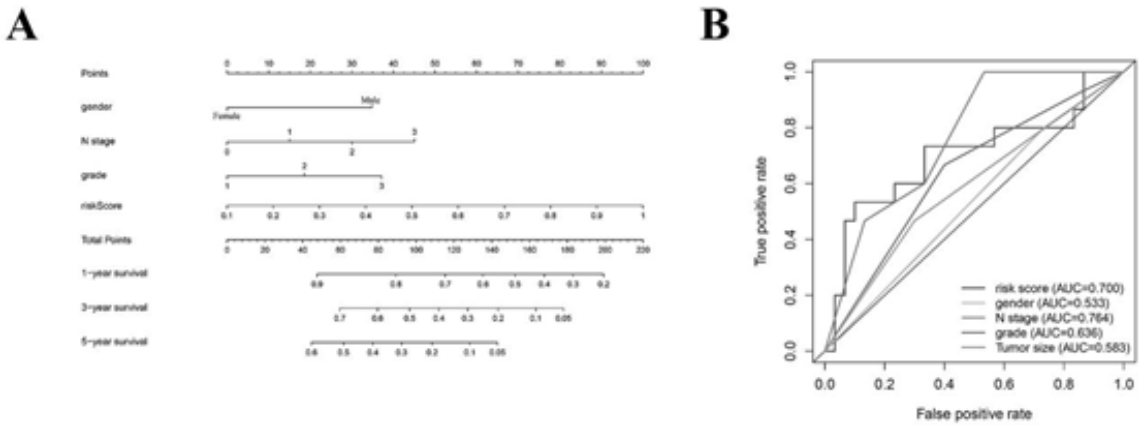

Fig. S3. The ROC curve and nomogram of GSE19417 prognostic model in EAC
The nomogram of GSE19417 model (Fig. S3A). The ROC curve of GSE19417 model (Fig. S3B)

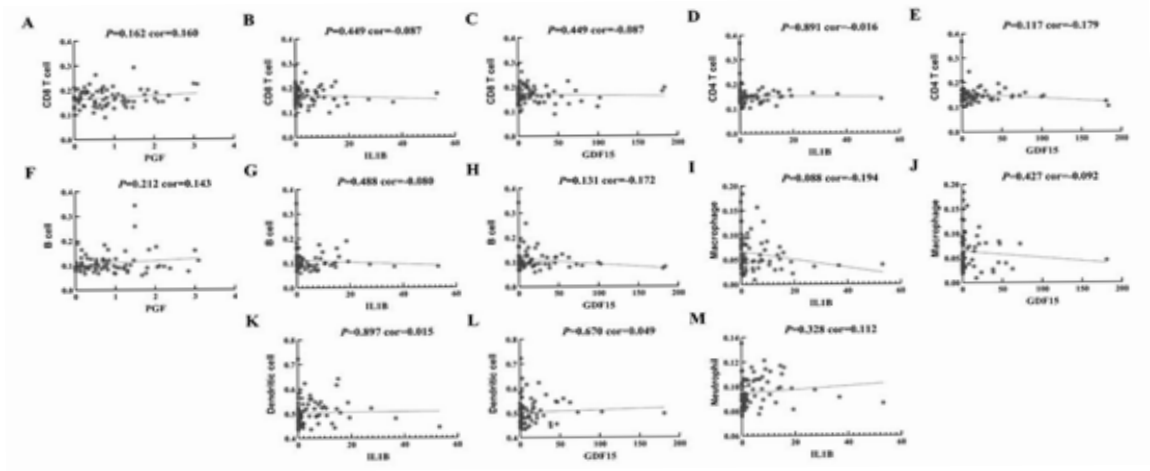

Fig. S4. Relationships between genes expression and infiltration abundances of six immune cells, including PGF with CD8 T cells (Fig. S4A), IL1B with CD8 T cells (Fig. S4B), GDF-15 with CD8 T cells (Fig. S4C), IL1B with CD4 T cells (Fig. S4D), GDF-15 with CD4 T cells (Fig. S4E), PGF with B cells (Fig. S4F, IL1B with B cells (Fig. S4G), GDF-15 with B cells (Fig. S4H), IL1B with microphage (Fig. S4I), GDF-15 with microphage (Fig. S4J), IL1B with DCs (Fig. S4K), GDF-15 with DCs (Fig. S4L), IL1B with neutrophils (Fig. S4M)

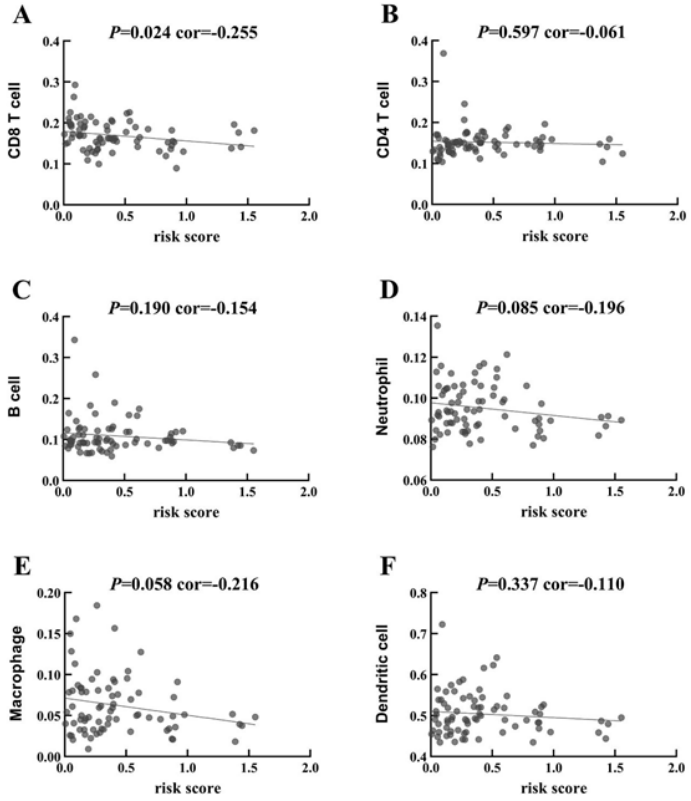

Fig. 8. Relationships between the prognostic model and infiltration abundances of B cells (Fig. 8A), CD4+ T cells (Fig. 8B), CD8+ T cells (Fig. 8C), dendritic cells (Fig. 8D), macrophages (Fig. 8E), neutrophils (Fig. 8F)

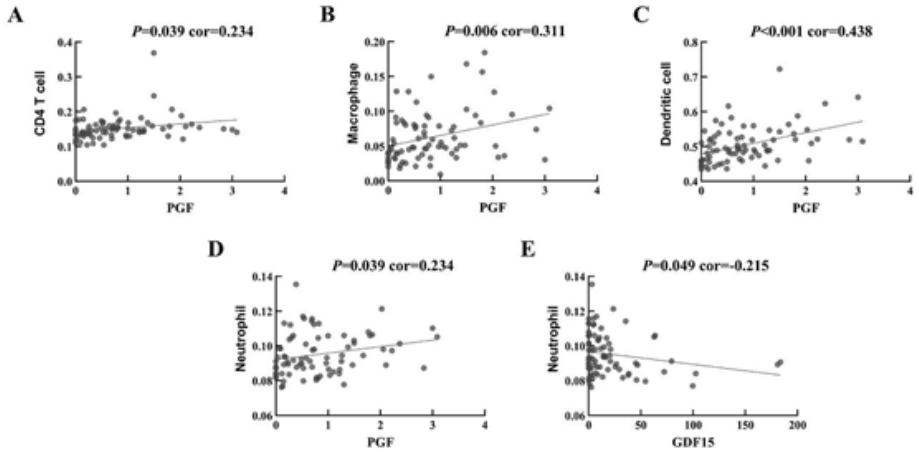

Fig. 9. Relationships between genes expression and infiltration abundances of immune cells, including PGF with CD4 T cells (Fig. 9A), PGF with macrophages CD4+ T cells (Fig. 9B), PGF with DCs (Fig. 9C), PGF with neutrophils (Fig. 9D), GDF-15 with neutrophils (Fig. 9E)

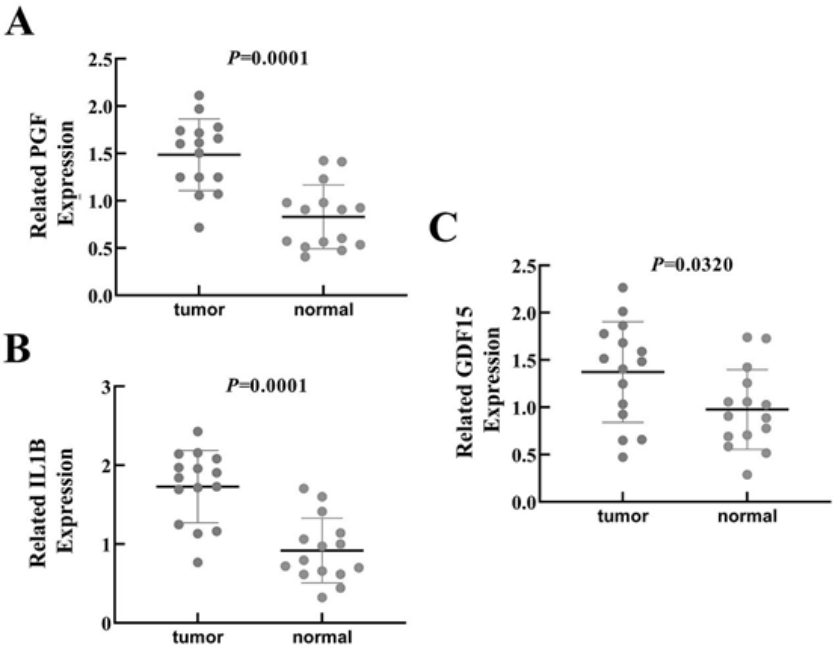

Fig. 10. The expression of PGF(Fig. 10A), IL1B (Fig. 10B)and GDF-15 (Fig. 10C) in tumor tissues with adjacent tissues.

be used as valuable clinical biomarkers in the occurrence and development of EAC. Here, the researchers screened three survival related IRGs (PGF, GDF15 and IL1B) in the prognostic model. PGF (previously known as PlGF), a member of the VEGF family, plays crucially in angiogenesis, progression and metastasis of EC (Fischer et al. 2008, Samadi et al. 2018). In the model, the researchers found that PGF positively regulated the infiltration of four cells including CD4+ T cells, dendritic cells, macrophages, neutrophils. Previously, the combination of PGF and VEGFR-1 is shown to promote tumour immune microenvironment and recruit macrophages to accelerate tumour progression (Incio et al. 2016). PGF can inhibit the activation and maturation of dendritic cells, thereby increasing the number of naive CD4 cells, these will seriously make the anti-tumor functionality of the immune system affected (Lin et al. 2007). Fisher et al. indicated that GDF-15 in EAC was significantly overexpressed than normal oesophagus and Barrett's oesophagus, the serum high GDF-15 level in patients with EAC had worse prognosis compared to low level patients (Fisher et al. 2008). In this article, the researchers found a negative correlation between GDF-15 expression and neutrophil infiltration. Previous studies have confirmed that, in a model of myocardial ischemia GDF-15 expression can inhibit neutrophil infiltration in inflammatory response, resulting in the myocardium protection (Zhang et al. 2016). In addition, GDF-15 can inhibit the survival of macrophages and the maturation of dendritic cells, attenuates the immune system against tumours, leading to tumour progression (Ratnam et al. 2017; Zhou et al. 2013). Currently, the research is limited on the role of GDF and neutrophils in tumours, and this may be a potential therapeutic target for esophageal adenocarcinoma immunotherapy. Studies by others have found that IL1B secreted by macrophages can promote esophageal cancer migration, invasion (Zhou et al. 2018). By using RT-PCR the researchers verified the expression of three genes in esophageal adenocarcinoma, which may provide potential therapeutic targets for esophageal adenocarcinoma.

To explore the molecular mechanism more deeply, the researchers investigated the biological functions of 259 IRGs. These genes mainly participate

in some GO terms related to extracellular function and immune defence response. KEGG analysis showed that these IRGs were mainly controlled cytokine-cytokine receptor interaction, chemokine signalling pathway, and viral protein interaction with cytokine and cytokine receptors. Most of the IRGs involved in the visual network are up-regulated genes. Of the pathways implicated, Chemokine signalling is involved in the whole process of tumour growth and metastasis, and its expression is related to prognosis (Rubin). The related chemokine/chemokine receptor axis is also considered to drive the transfer process (Bonecchi et al. 2009). It is possible for IL-17 cytokines to become a new target for anti-cancer therapy in some studies (Chang and Chen 2011). In addition, the abnormalities of MAPK and PI3K signalling pathways have been reported to act in tumour growth, proliferation and metastasis (Pappalardo et al. 2016; Xu et al. 2014). And down-regulating the PI3K / Akt signalling pathway is capable of inhibiting proliferation and promoting apoptosis of esophageal cancer cells (Li et al. 2007). The blocking of the MAPK pathway can also significantly make the proliferation restrained and apoptosis induced in esophageal cancer cells (Wu et al. 2016).

Furthermore, the researchers established an immune-based prognostic model. In this study, OS was used as a predictive endpoint, which is suitable for survival monitoring of patients with EAC. In fact, IRG-based risk score (IRGRS) can function as a prognostic indicator as well as refract the immune status of the body. In this investigation, the AJCC stage, N stage and the risk score owned vital prognostic significance based on other parameters that were adjusted, like gender and T stage. In EAC, the risk score could independently act as a predictor. Further, The researchers analyzed and observed that risk score negatively controlled the CD8+ T cell infiltration, which is similar with the possibility that there is more CD8 + T cell infiltration in low-risk EAC patients. Previous studies indicated that CD8 + T cells have anti-tumour effects, which can directly lyse tumour cells in vivo after differentiation into cytotoxic T cells (CTLs) (Gutschner and Diederichs 2012; Johnston et al. 2014). As it is known, activated CD8+ T cells can highly express fasl, and almost all cancer cells express Fas receptors (Chen et al. 2013). CD8+ T cells has been reported to be associated with a good prognosis of esophageal cancer by regulating immune response (Song et al. 2007), and the researchers revealed consistent findings in this study.

Deeply, the researchers identified prognostic immune genes through the TCGA database and established a prognostic model. Further, the prognostic risk score was discovered to be negatively related with CD8+ T cells, providing some basis for the prognosis and immunological therapy of EAC in the near future. However, the current research has some limitations. Firstly, it is still indistinct for the action of some genes among the prognosis-related genes in EAC. In the future research, the researchers would further explore the role of some genes in EAC. Secondly, in order to further apply the model to clinical practice, in vitro or in vivo experiments are widely needed .

CONCLUSION

As far as it is known, this is the first time for the researchers to carry out an immunogenomic landscape analysis. In the current study, the researchers identified several prognostic IRGs and built an IRGs-related prognostic model in EAC. CD8+ T cell infiltration positively correlated with the outcome of EAC patients, offering a more full-scale insight of the action of immunological response in the aspect of tumour micro-environment and then giving some novel ideas for enhancing the prognosis outcome and immune therapy of EAC.

RECOMMENDATIONS

IL1B, FABP2, GDF-15, MAPT, PGF, TNFSF18, IL17RB, RORC, HSPA6 and HSP90AA1 can be used in the IRGs-related prognostic model to predict the IRGs-related prognostic model.

AVAILABILITY OF DATA AND MATERIAL

Currently, all datasets generated and/or analysed are available in the TCGA data portal (https://tcga-data.nci.nih.gov/tcga/).

COMPETING INTERESTS

The authors claim no conflicts of interest regarding the study or the manuscript.

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AUTHOR CONTRIBUTIONS

Dr. JJW and WJW contrived the study and prepared the paper. Dr. XYC and XW conducted research in this study. The literature searching and related analyses were performed by Dr. LX and PPZ. Dr. XX, YYD and KC took on the statistical analysis. All authors reviewed the final manuscript and approved it.

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