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Research Article

Construction of a Platelet-Related Gene Signature for Predicting Prognosis and Drug Sensitivity in Colorectal Cancer

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Background: Colorectal cancer (CRC) ranks among the most prevalent forms of cancer and is a significant contributor to cancer-related mortality globally. Platelets play a crucial role in tumor biology by interacting with various immune cells, influencing multiple biological processes.
Methods: We utilized datasets from TCGA, GSE17536, GSE39582, and GSE103479 to develop a platelet-related gene signature (PRS) using least absolute shrinkage and selection operator (LASSO) analysis. The effectiveness of PRS in predicting responses to immunotherapy was assessed using three immunotherapy datasets (GSE91061, GSE78220, and IMvigor210) and several predictive scores.
Results: The PRS demonstrated robust performance in forecasting the survival outcomes of CRC patients. In the TCGA cohort, the areas under the ROC curves for 1-, 3-, and 5-year survival were 0.845, 0.849, and 0.785, respectively. Further analysis identified PRS as an independent risk factor for CRC patients. A nomogram was constructed to predict clinical outcomes for CRC patients. Additionally, a lower PRS score was associated with higher TMB scores, elevated PD1 and CTLA4 immunopheno scores, reduced TIDE and immune escape scores, higher response rates, and more favorable clinical outcomes, suggesting better immunotherapy responses. Conversely, lower PRS scores correlated with increased IC_{50} values for certain drugs used in chemotherapy and targeted therapy. Patients in the high-risk group exhibited elevated gene set scores related to cancer hallmarks such as Notch signaling, hypoxia, and glycolysis.
Conclusion: Our study established a PRS for CRC that serves as a valuable tool for predicting prognosis, stratifying risk, and guiding treatment decisions for CRC patients.

Keywords: colorectal cancer; immunotherapy; platelet; prognostic signature; TCGA

1. Introduction

Colorectal cancer (CRC) is one of the most common types of cancer and a leading cause of cancer death worldwide [1]. There are an estimated 1,880,000 new cases of CRC and 915,000 CRC-related deaths worldwide [2]. At present, despite radical surgery combined with chemo- and radiotherapy for the management of CRC, many patients experience drug resistance, recurrence, and metastasis, which are the main causes of CRC-related death [3]. For decades, the TNM staging system has been the gold standard for evaluating the clinical outcome of CRC. However, many CRC cases at the same stage have varied clinical prognoses, demonstrating the shortcomings of the TNM staging system in predicting the prognosis of CRC patients [4]. Immunotherapy was suggested as a major treatment modality for CRC [5]; however, limited biomarkers could be used for predicting the immunotherapy benefits of patients.

The challenge in CRC immunotherapy lies in the fact that only a small fraction of patients with MSS tumors

benefit from immune checkpoint inhibitors. Current research has focused on overcoming this limitation by exploring combination therapies, including combining ICIs with chemotherapy, targeted therapy, and anti-angiogenic agents. While early-phase clinical trials have shown promise, these combination therapies often result in modest improvements in survival and response rates, especially in patients with advanced or metastatic CRC [6–8]. Moreover, not all patients who receive immunotherapy, including those with MSI-H tumors, achieve long-lasting responses, leading to tumor relapse or resistance over time. This necessitates a better understanding of the molecular mechanisms driving resistance to immunotherapy in CRC. This evidence suggested the urgent need for biomarkers for predicting the prognosis and immunotherapy benefits.

Platelets are one of the main subtypes of blood cells that are correlated with hemostasis and thrombosis [9]. Patients would spot bleeding, bruising, and purple spots when platelets reduced. A severely reduced platelet count may result in bleeding in the brain or lung [10]. Studies have revealed the important functions of platelets in cancer. In many solid cancers, the platelets were increasing, which may result in secreting cytokines and boosting tumor growth and angiogenesis [11]. By releasing vascular endothelial growth factor (VEGF), platelets engaged in the angiogenesis and tumor progression [12]. Moreover, platelets showed significant correlation with the drug sensitivity in chemotherapy and immunotherapy [13–15]. Platelets were involved in many biological processes in tumors via the interaction of the many immune cells [16, 17]. In CRC, platelets have been shown to influence tumor growth through multiple mechanisms. A growing body of evidence suggests that platelets promote CRC progression by facilitating tumor cell proliferation, survival, and migration. For instance, platelets release various growth factors such as VEGF, platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β), all of which contribute to angiogenesis and tumor vascularization [18, 19]. Platelets interact with tumor cells to promote the formation of the pre-metastatic niche and increase the ability of tumor cells to invade distant organs in CRC [20]. Additionally, platelets have been implicated in modulating the immune system, promoting an immunosuppressive microenvironment that allows tumors to evade immune surveillance in CRC [21]. Thus, it is necessary to fully elucidate the role of platelet-related genes (PRGs) in CRC.

After obtaining PRGs from databases, we developed a platelet-related gene signature (PRS) using the data from four datasets, including one dataset from the Cancer Genome Atlas (TCGA) and three datasets from Gene Expression Omnibus (GEO). The role of PRS in predicting the prognosis, immune infiltration, and therapy benefits in CRC was also evaluated.

2. Materials and Methods

2.1. Datasets Sources and Identification of differentially Expressed Genes. From TCGA dataset ($n = 402$), GSE17536 ($n = 172$), GSE39582 ($n = 560$), and GSE103479 ($n = 150$) dataset, we downloaded mRNA data of CRC for PRS construction. Another three datasets, IMvigor210 dataset ($n = 298$), GSE91061 ($n = 98$), and GSE78220 ($N = 28$), obtained from the GEO database, were selected as an immunotherapy cohort for evaluating the role of PRS in predicting the immunotherapy benefits. Limma packages were used to identify differentially expressed genes (DEGs) between in CRC with |Log2FC| value > 1.5 and P value < 0.05 as the cut-off. PRGs were collected from gene set enrichment analysis (GSEA) gene sets (https://www.gsea-msigdb.org/gsea/index.jsp/) with "platelet" as the researching keyword and a total 480 PRGs were obtained in our study (Supporting Table 1).

2.2. Construction of the PRS and Predictive Nomogram. Potential prognostic markers among PRGs in CRC were identified by univariate Cox regression analysis. To construct the PRS, we performed least absolute shrinkage and selection operator (LASSO) analysis using the glmnet R package. Following the identification of PRS candidates and their corresponding coefficients, we calculated the risk score for each HCC case. The CRC samples were subsequently divided into high- and low-risk groups based on the optimal cut-off value determined using the survminer R package. To assess the predictive performance of PRS for clinical outcomes in CRC patients, we generated ROC curves and calculated the C-index using the survivalROC R package. Univariate and multivariate Cox regression analyses were conducted to identify risk factors associated with overall survival (OS) rates in CRC patients. Additionally, a predictive nomogram was developed to estimate the 1-, 3-, and 5-year OS rates of CRC patients using the nomogramEx R package. The accuracy of the nomogram predictions was evaluated by comparing actual versus predicted survival outcomes through calibration curves.

2.3. Immune Infiltration Analysis. The ESTIMATE method was used to determine the immune score and ESTIMATE score of each CRC case [22]. The abundance of immune cells in CRC was determined by seven methods, all of which have unique properties and strengths [23]. Gene set scores involved in immune cells and immune functions-related of CRC cases were calculated using the single-sample gene set enrichment analysis (ssGSEA) method with the "GSVA" package. Relative expression of human leukocyte antigen (HLA)-related genes and immune checkpoints in different risk score groups was visualized with the "ggpubr" or "ggplot" R package.

2.4. Therapy Benefits Analysis. To evaluate the performance of the PRS in predicting immunotherapy response in CRC patients, we utilized several predictive scores. These included:

1. Tumor Immune Dysfunction and Exclusion (TIDE) Score: Obtained from the TIDE platform (http://tide.dfci.harvard.edu/).

2. Immunopheno Score: Retrieved from The Cancer Immunome Atlas (https://tcia.at/home).
3. Immune Escape Score: Derived from a previous study [24].
4. Tumor Mutation Burden (TMB) Score: Calculated to assess genetic alterations.

Lower TIDE and immune escape scores, along with higher immunopheno scores and TMB scores, indicated a reduced likelihood of immune escape and better effectiveness of immunotherapy treatment.

Additionally, data from the Genomics of Drug Sensitivity in Cancer (GDSC) database (https://www.cancerrxgene.org/) were used to calculate the IC_{50} values for various drugs in each CRC case using the "oncoPredict R" package. A higher IC_{50} value signified lower drug sensitivity.

Similar methods could be found in previous studies [25, 26].

3. Results

3.1. Identification of Potential Prognostic Biomarkers. Compared with normal tissues, we identified 5084 DEGs in CRC tissues with $|\text{Log fold change}| \geq 1.5$ and p value < 0.05 as the cutoff (Figure 1(a)). These DEGs contained 165 PRGs (Figure 1(b)). By performing univariate Cox regression analysis, we found 29 potential prognostic biomarkers in CRC (Figure 1(c), $p < 0.05$).

3.2. Machine Learning Developed a Prognostic PRS. Potential prognostic biomarkers were submitted to perform LASSO regression analysis, with which we constructed a PRS containing 19 genes. The coefficient and partial likelihood deviance of PRS is shown in Figure 1(d). The risk score of each CRC case was calculated using the following formula: Risk score = $(-0.1193) * F2RL2^{exp} + 0.0434 * GNGT1^{exp} + 0.3198 * PTPN6^{exp} + (-0.0374) * KIF20A^{exp} + (-0.0391) * SERPINA1^{exp} + 0.1530 * TIMP1^{exp} + 0.0327 * ADRA2B^{exp} + (-0.4070) * TUBA1C^{exp} + (-0.2643) * ABHD6^{exp} + (-0.0935) * GLA^{exp} + (-0.0246) * GNG5^{exp} + 0.0905 * GP6^{exp} + (-0.1382) * MANF^{exp} + 0.1815 * TUBB2A^{exp} + (-0.2794) * ASAH1^{exp} + (-0.0678) * CAP1^{exp} + (-0.4844) * PRKAR2A^{exp} + 0.1018 * VAV2^{exp} + (-0.012) * TMSB4X^{exp}$. We then clustered CRC cases into high and low PRS score groups. Further analysis showed that CRC patients with a high risk score experienced an unfavorable survival outcome with AUCs of 1-year, 3-year, and 5-year ROC of 0.845, 0.849, and 0.785 in the TCGA cohort; 0.670, 0.747, and 0.731 in the GSE17536 cohort; 0.667, 0.721, and 0.762 in the GSE39582 cohort; and 0.686, 0.738, and 0.775 in the GSE103479 cohort, respectively (Figures 1(e), 1(f), 1(g), 1(h), all $p < 0.05$).

3.3. The Performance of PRS in Evaluating the Prognosis of CRC Patients. To compare the performance of the PRS with other clinical characteristics in evaluating the prognosis of CRC patients, we calculated the C-index for PRS and various clinical features (age, gender, tumor grade, and clinical stage). Our analysis revealed that the C-index of PRS was significantly higher than that of the clinical characteristics in both the TCGA and GEO cohorts (Figure 2(a)). Further univariate and multivariate Cox regression analyses confirmed PRS as an independent risk factor for survival outcomes in CRC patients within the TCGA and GEO datasets (Figures 2(b), 2(c), all $p < 0.05$). To enhance the prediction of clinical outcomes for CRC patients, we developed a nomogram (Figure 2(d)). As illustrated in Figure 2(e), the nomogram demonstrated excellent agreement between predicted and actual observed survival rates at 1, 3, and 5 years in the TCGA cohort. These findings underscore the robust and consistent performance of PRS in predicting clinical outcomes for CRC patients.

3.4. Dissection of PRS-Based Tumor Immune Microenvironment. The correlation between the PRS score and immune cell infiltration in CRC is illustrated in Figure 3(a). Specifically, a negative correlation was observed between the risk score and the levels of immune-activated cells, including CD8+ T cells, CD4+ T cells, and dendritic cells (Figures 3(b), 3(c), 3(d), $p < 0.05$). ssGSEA revealed that patients with a lower PRS score exhibited higher abundances of B cells, CD8+ T cells, neutrophils, and tumor-infiltrating lymphocytes (TILs) in CRC (Figure 3(e)). In patients with a high PRS score, gene set scores related to APC co-stimulation, cytolytic activity, inflammation promotion, and T cell co-stimulation were downregulated (Figure 3(f)). Additionally, CRC patients with a high PRS score showed lower stromal scores, immune scores, and ESTIMATE scores (Figure 3(g), all $p < 0.05$).

3.5. PRS as an Indicator for Predicting Therapy Benefits in CRC. The data suggested a lower expression of immune checkpoints and HLA-related genes in CRC patients with high-risk scores (Figures 4a, b, all $p < 0.05$). As shown in Figures 4c, d, a lower risk TMB score and PD1&CTLA4 immunopheno score were found in CRC patients with a low-risk score ($p < 0.05$). Further analysis suggested that CRC patients with low risk scores had a lower intratumoral heterogeneity score, lower immune escape, lower TIDE score, and lower T cell dysfunction score (Figures 4e, f, g, all $p < 0.05$).

A higher immunopheno score indicated a greater potential for benefiting from immunotherapy [27]. Conversely, a higher TIDE score suggested a reduced likelihood of immune escape and improved response to immunotherapy [28, 29]. Elevated expression of HLA-related genes and immune checkpoints implied broader antigen presentation, thereby increasing the chances of successful immunotherapy [30]. Therefore, CRC patients with a low-risk score may experience better outcomes from immunotherapy.

To validate these findings, we analyzed three immunotherapy datasets: GSE91061, GSE78220, and IMvigor210. In the GSE91061 dataset, which included cutaneous melanoma patients receiving anti-PD-L1 therapy, responders exhibited significantly lower risk scores compared to nonresponders (Figure 4(h), $p < 0.01$). This data indicated more favorable clinical outcomes for patients with lower risk scores

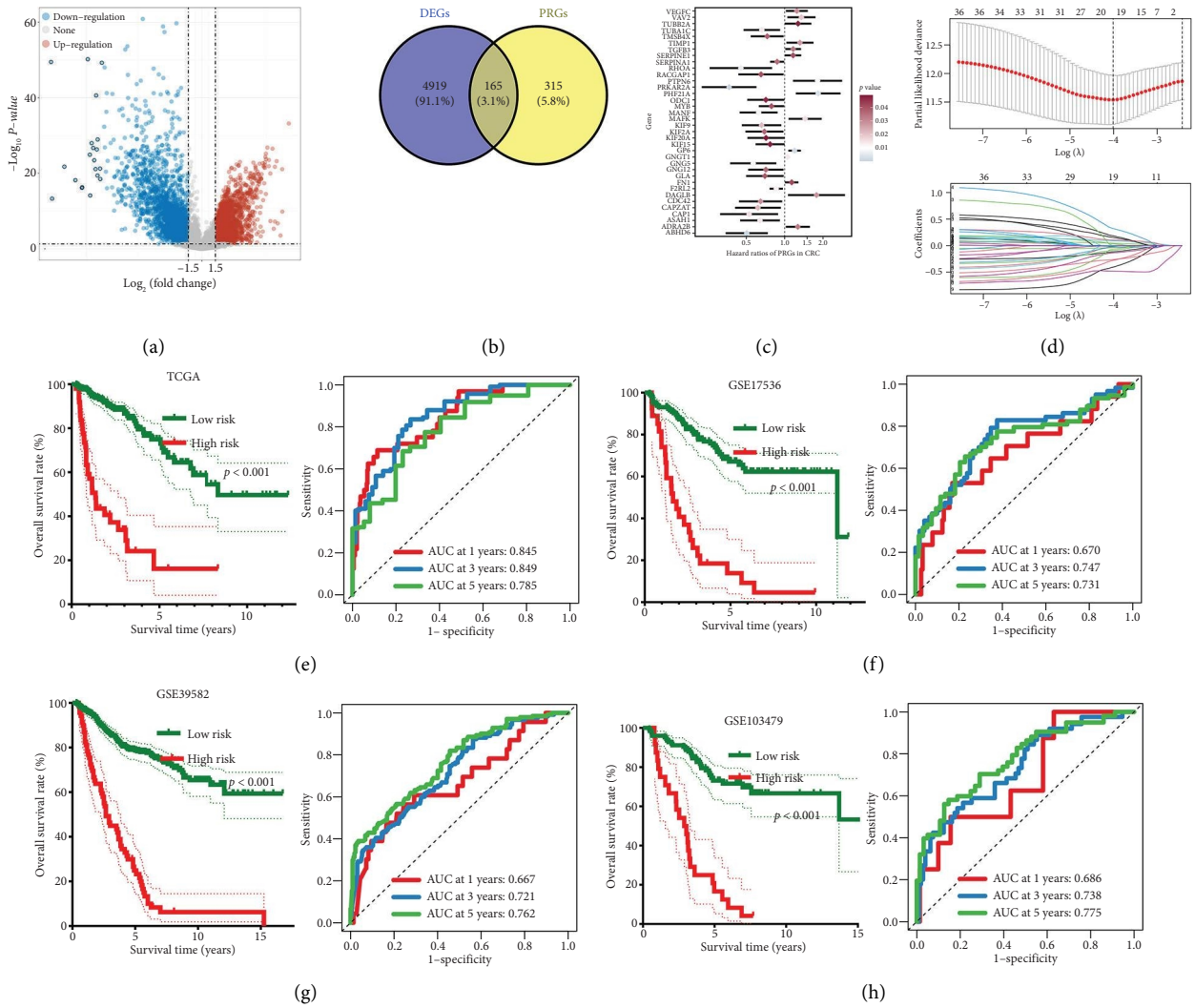


FIGURE 1: Construction of a platelet-related signature in CRC. (a) Differentially expressed genes in CRC in the TCGA cohort. (b) The overlap between differentially expressed genes and platelet-related genes. (c) Potential biomarkers identified using univariate Cox analysis. (d) The coefficient and partial likelihood deviance of PRS. The survival curve and corresponding ROC curve of CRC with high- and low-risk scores in TCGA (e), GSE17536 (f), GSE39582 (g), and GSE103479 (h) cohorts.

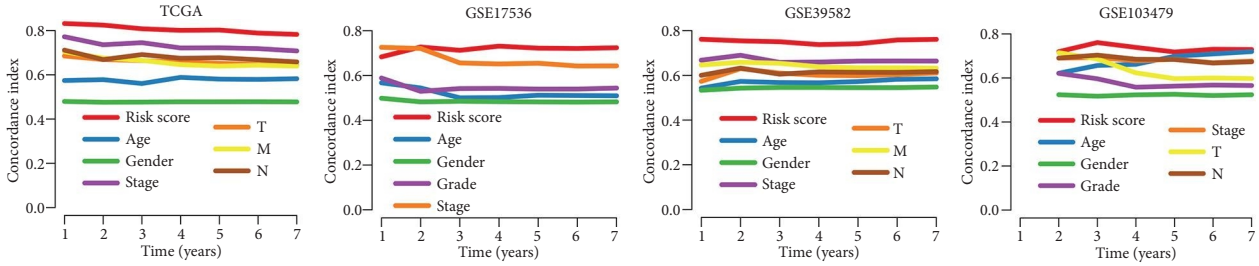
($p = 0.006$), while those with higher risk scores showed a lower response rate ($p < 0.05$). Consistent results were observed in both the GSE78220 and IMvigor210 cohorts (Figures 4(i), 4(j)).

Additionally, we examined the IC_{50} values of common drugs used in chemotherapy and targeted therapy, given their critical role in CRC treatment. Our analysis revealed that CRC patients with a low risk score had lower IC_{50} values for several drugs, including oxaliplatin, 5-fluorouracil, irinotecan, bevacizumab, cetuximab, and panitumumab (Figures 5a, b). This suggests that patients with low-risk scores exhibit greater sensitivity to chemotherapy and targeted therapies.

3.6. Difference in Functional Enrichment in Different PRS Score Groups. We investigated the functional enrichment differences between different PRS score groups to elucidate how PRS-related genes contribute to the development of bladder cancer. As illustrated in Figure 6, the high-risk score group exhibited elevated gene set scores in several key pathways, including peroxisome, P53 pathway, notch signaling, IL2-STAT5 signaling, hypoxia, glycolysis, DNA repair, coagulation, angiogenesis, and mTORC1 signaling in CRC (all $p < 0.05$).

4. Discussion

In this study, we developed a PRS for CRC using the LASSO method. Further analysis revealed that PRS serves as an independent risk factor for stomach adenocarcinoma (STAD) patients and demonstrates robust performance in predicting OS rates. Additionally, our findings indicated that PRS can be a valuable indicator for predicting immunotherapy benefits. Specifically, a lower PRS score was associated with better responses to immunotherapy, suggesting improved clinical outcomes for patients with lower PRS scores.



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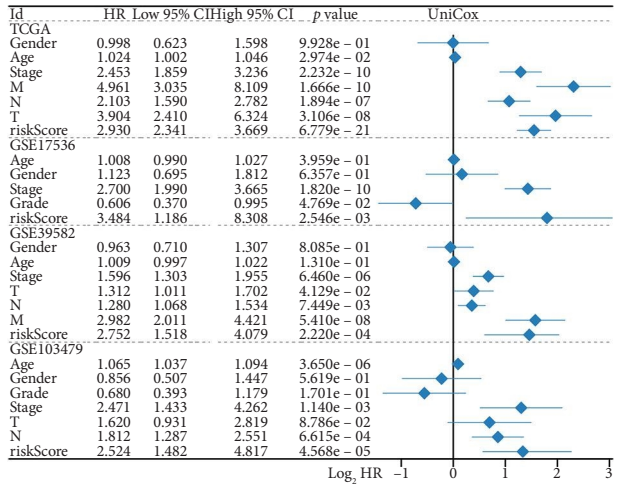

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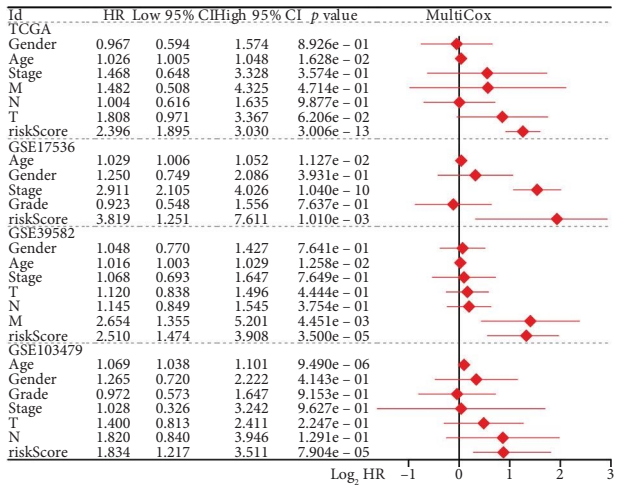

(c)

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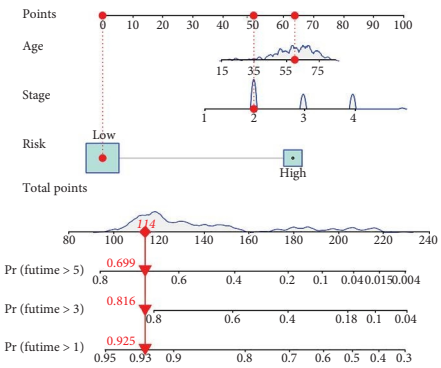
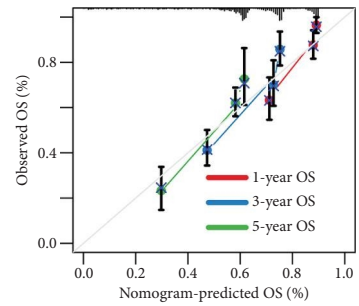
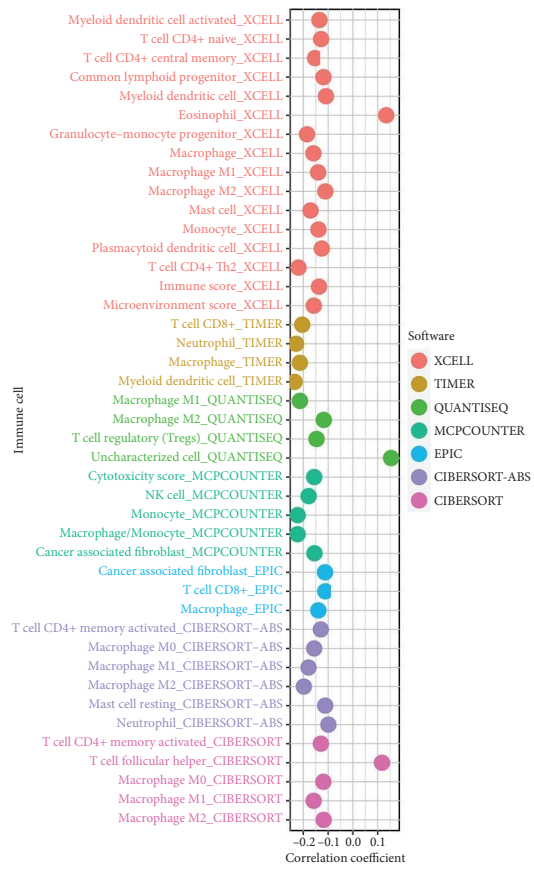


(d)

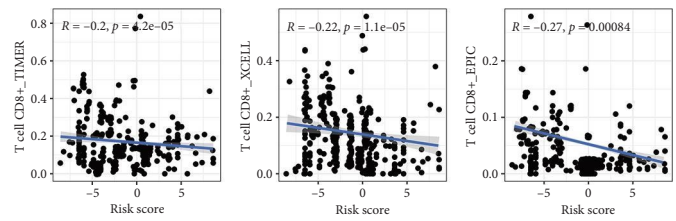


(e)

Figure 2: The performance of PRS in evaluating the prognosis of CRC patients. (a) The C-index of PRS and clinical characters in predicting the prognosis of CRC patients. (b), (c) Risk factors in CRC identified by univariate and multivariate Cox regression analysis. (d), (e) Predictive nomogram and calibration evaluating the survival outcome of CRC patients.



(a)



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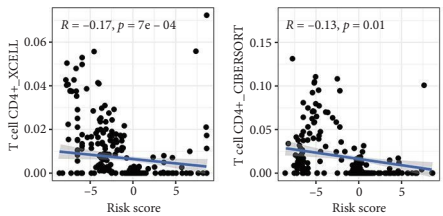

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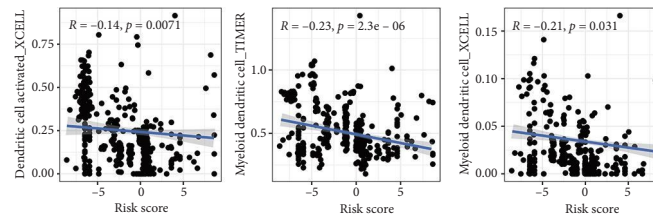

(d)

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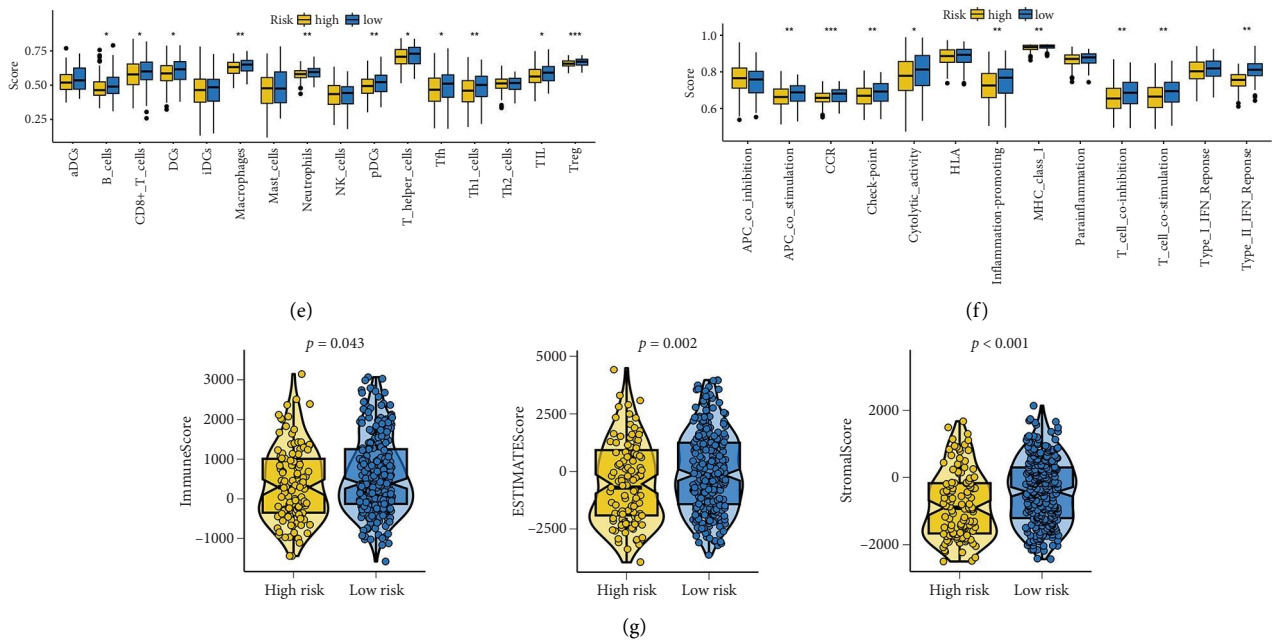
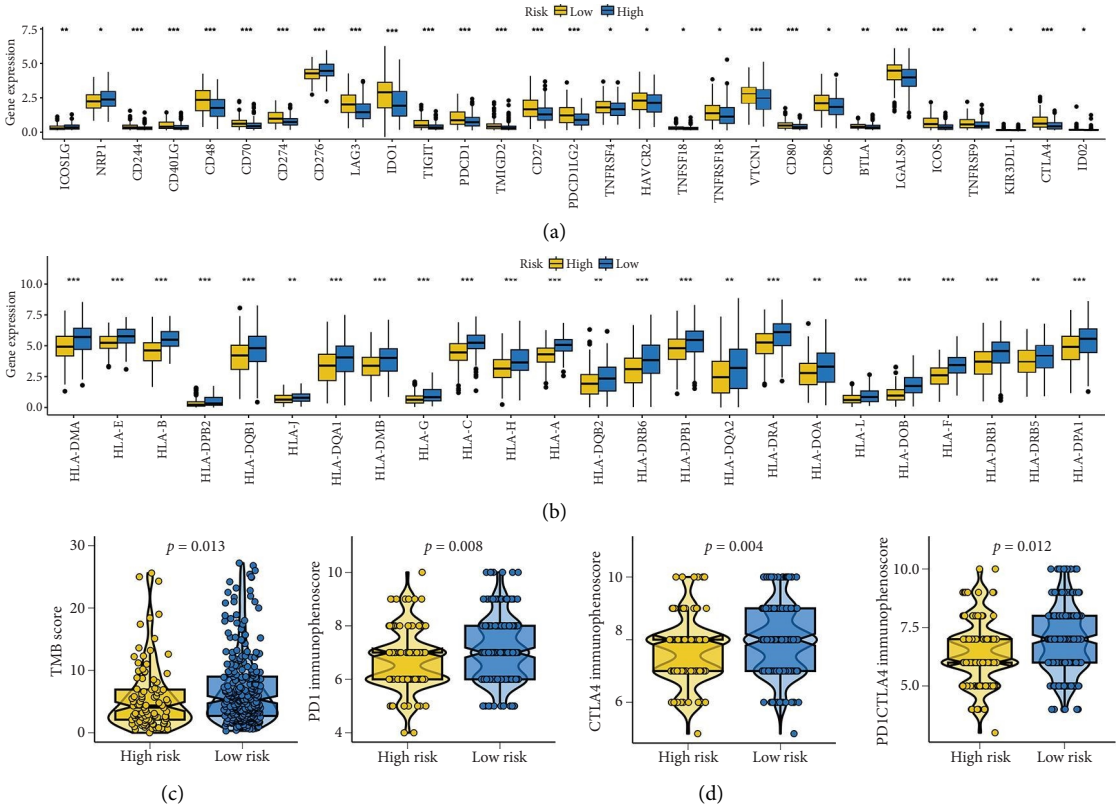


Figure 3: PRS-based immune infiltration atlas in CRC. (a) Seven state-of-the-art algorithm-based correlation atlases between PRS and immune cells in CRC. (b)–(d) The association between PRS score and CD8+ T cell, CD4+ T cell, and dendritic cells. The relative level of immune cells (e), immune-related functions (f), and ESTIMAE score (g) in different PRS score groups. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.



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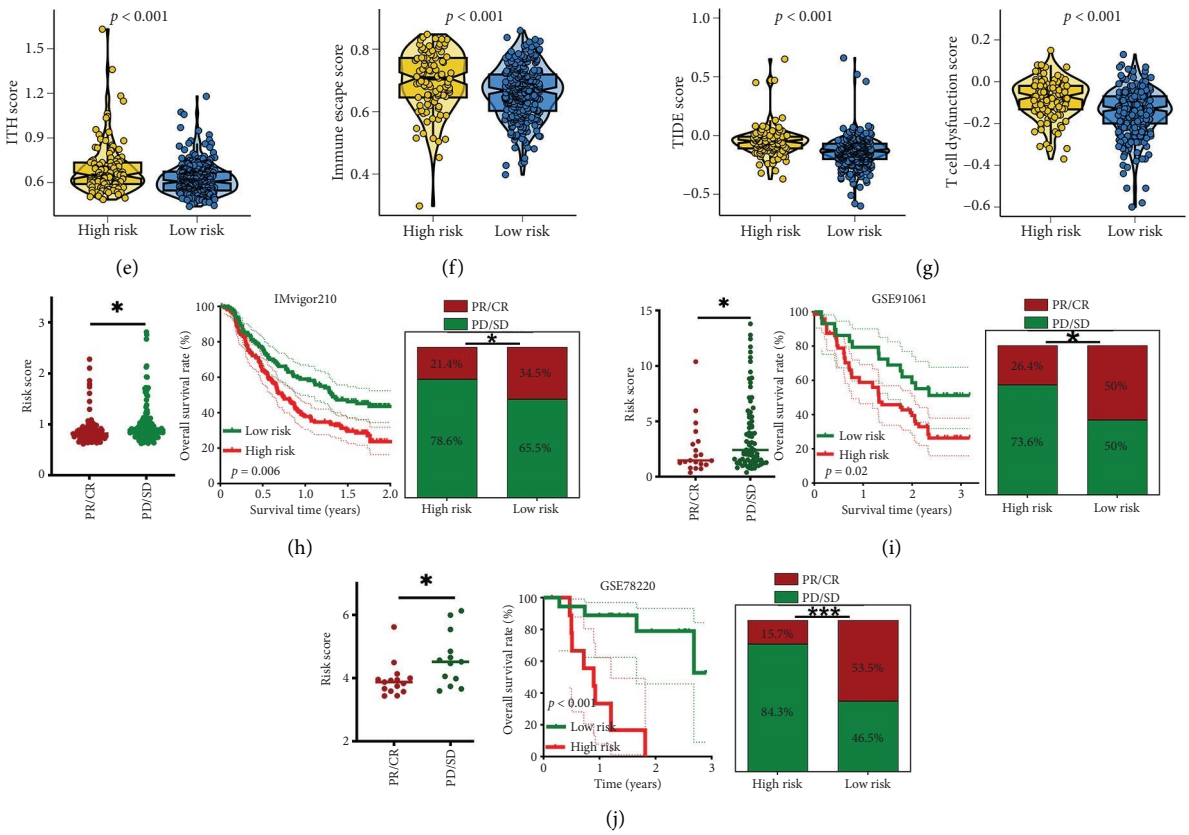

FIGURE 4: PRS acted as an indicator for predicting the immunotherapy benefits in CRC. The level of immune checkpoints (a), HLA-related genes (b), TMB score (c), PD1&CTLA4 immunopheno score (d), ITH score (e), immune escape (f), and TIDE score (g) in different PRS score of CRC patients. The immunotherapy response and overall rate in patients with high and low PRS scores in IMvigor210 (h), GSE91061 (i), and GSE78220 (j) datasets. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

The PRS was constructed with 19 genes, including F2RL2, GNGT1, PTPN6, KIF20A, SERPINA1, TIMP1, ADRA2B, TUBA1C, ABHD6, GLA, GNG5, GP6, MANF, TUBB2A, ASAH1, CAP1, PRKAR2A, VAV2, and TMSB4X. PTPN6 enhances chemosensitivity of tumor cells by inhibiting the SP1/MAPK signaling pathway in CRC [31]. KIF20A accelerated cellular malignant behavior and promotes chemosensitivity by regulating the JAK/STAT3 signaling pathway in CRC [32]. SERPINA1 promotes tumor progression and correlates with poor clinical outcomes in CRC [33]. TIMP1 inhibited sorafenib-triggered ferroptosis by activating the PI3K/Akt signaling pathway in CRC [34]. ABHD6 inhibited tumor progression by the AKT signaling pathway in CRC [35]. CAP1 mediates the cyclic AMP signals that activate Rap1 in stimulating matrix adhesion in CRC [36].

Our study revealed that the PRS functions as an independent risk factor in CRC and demonstrates robust performance in predicting OS rates. Interestingly, PRS has shown broader applicability across various cancer types. For instance, in triple-negative breast cancer, PRS was effective in predicting prognosis and identifying drug sensitivity genes [37]. Additionally, PRS has been utilized to forecast outcomes in pancreatic adenocarcinoma [38]. Furthermore, PRS serves as a prognostic biomarker in hepatocellular carcinoma [39].

Immunotherapy plays a crucial role in the therapeutic strategy for CRC patients [40, 41]. Our study revealed that CRC patients with a high-risk score exhibited higher TIDE scores, higher immune escape scores, lower PD1 and CTLA4 immunopheno scores, lower TMB scores, lower response rates, and poorer clinical outcomes. Previous research has indicated that TMB serves as an important predictor of immunotherapy benefits, with higher TMB scores being associated with better responses to immunotherapy [42, 43]. Additionally, patients with elevated TIDE scores are more likely to experience immune escape [28]. Therefore, PRS may serve as a valuable indicator of immunotherapy benefits in CRC. Specifically, patients with low-risk scores are more likely to benefit from immunotherapy, exhibiting better clinical outcomes.

We investigated the differences in functional enrichment between different PRS score groups to better understand how PRS-related genes contribute to the development of CRC. Our analysis revealed that the high-risk score group exhibited elevated gene set scores in several key pathways, including hypoxia, glycolysis, DNA repair, coagulation, and angiogenesis in CRC. Epithelial NOTCH signaling remodels the tumor microenvironment and drives poor prognosis subtypes and metastasis [39]. The NOTCH signaling pathway is crucial for regulating platelet production,

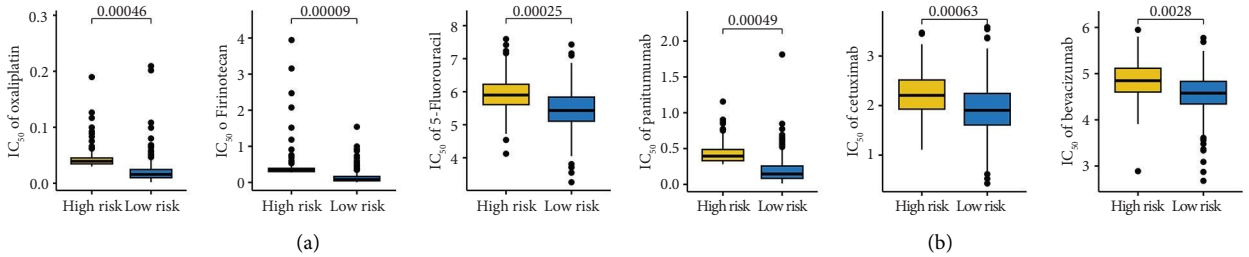

Figure 5: Drug sensitivity analysis. Lower PRS scores correlated with a lower IC_{50} value of common drugs in chemotherapy (a) and targeted therapy (b).

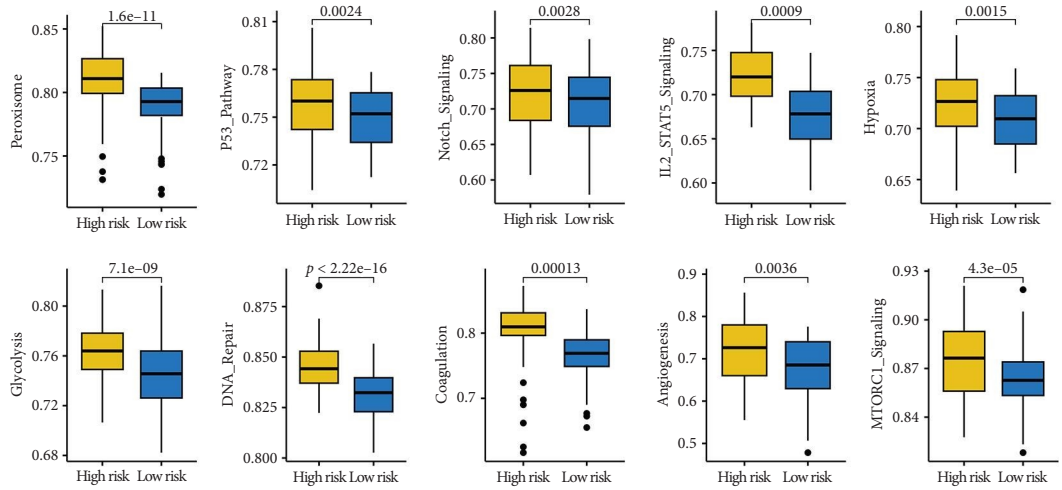

Figure 6: PRS-based function analysis in CRC. The relative gene set score correlated with cancer hallmarks in different PRS score groups in STAD.

differentiation, and function. Platelet-related genes, such as PTPN6, have been shown to modulate Notch signaling, influencing platelet activation and aggregation [44]. Hypoxia was correlated with tumor initiation and progression in CRC [45]. Hypoxia is a key factor in tumor progression and is linked to platelet activation. Platelets have been shown to contribute to tumor angiogenesis by secreting hypoxia-inducible factors (HIFs) and other cytokines that stimulate the growth of new blood vessels [46]. Platelets are directly involved in the angiogenesis process by releasing factors like VEGF and PDGF. In CRC, elevated platelet levels are often associated with increased angiogenesis, which contributes to tumor vascularization and metastasis. Platelet-related genes like TUBA1C and GP6 play crucial roles in regulating platelet aggregation and the release of proangiogenic factors [47]. Enrichment in these pathways suggests that platelets actively support tumor growth by promoting blood vessel formation and enhancing nutrient and oxygen delivery to the tumor. Glycolysis played a vital role in liver metastases and histone lactylation in CRC [48]. The enrichment of specific pathways related to platelet function, including Notch signaling, hypoxia, glycolysis, angiogenesis, and mTORC1 signaling, provides valuable insight into the role of platelets in CRC progression and drug sensitivity. These pathways are directly involved in tumor growth, immune evasion, and resistance to therapy, making them essential for predicting prognosis and response to treatment in CRC patients. Understanding the mechanistic role of these pathways in the context of platelet-related genes helps refine predictive models, offering new opportunities for targeted therapeutic interventions in CRC.

4.1. Limitations. There were certain limitations on our investigation. The PRS in testing and training cohorts were retrieved from several databases. Heterogeneity could still exist even if the data were standardized before analysis. There was no internal clinical cohort to validate the PRS. To make sure that our findings are reliable, it would be preferable to carry out research in additional cell lines or to confirm the roles of additional genes of PRS.

5. Conclusion

Our investigation developed a PRS in CRC. The PRS acted as an indicator for predicting the prognosis, stratifying risk, and guiding treatment for CRC patients.

Data Availability Statement

This study received availability of data and materials from the TCGA dataset (https://tcga-data.nci.nih.gov/tcga/) and GEO (https://www.ncbi.nlm.nih.gov/gds).

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Yufang Wang: writing–original draft preparation, investigation, and formal analysis. Junjie Yang: data curation and writing–review and editing. Xiaofang Xu: conceptualization and resources. Tao Yu: methodology, supervision, software, validation, and project administration.

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The authors have nothing to report.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

Supplementary Table 1. The information of 480 genes related to platelets.

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