**Comprehensive Prognostic Risk Model Incorporating Tumor Microenvironment Genes for Colorectal Cancer**

**Introduction:**

Colorectal cancer (CRC) is a significant universal health problem, with diagnosis changing widely depending on patients. Colorectal cancer (CRC) was the third among all cancers causing death worldwide. Based on the GLOBOCAN data of 2022 released by the World Health Organization’s International Agency for Research on Cancer (WHO-IARC), each year around 1.92 million new colorectal cancer cases were identified and more than 904,019 deaths were recorded worldwide. Among the different cancer types, colorectal cancer ranks fourth and third respectively in the incidence and mortality with colorectal cancer incidence around 18.4% of the total cancer incidence, and mortality accounting for 8.2% of the total deaths [1]. The number of colorectal cancer cases was predicted to upsurge in 2030 by more than 60% resulting in 2.2 million fresh CRC cases and the death due to CRC will be 1.1 million [2].

The main treatment method for colorectal cancer patients was surgical resection in which the cancerous tissue is removed by surgery. The treatment at an early stage has been improved by the application of colonoscopy resulting in better clinical outcomes for colorectal cancer in many countries [3]. Many colorectal cancer patients developed the spread of their malignancy to the nearby tissues even though the cancerous tissues were completely removed by surgical resection [4]. There is a need for an effective and analytical evaluation system for more accurate and precise treatment for colorectal cancer. Even though the present prognostic models include clinical and molecular aspects, they repeatedly fail to get the complete intricate interaction between tumor cells and their microenvironment, which has a significant role in disease development and its response to treatment.

The colorectal cancer genetic basis model explained the heterogeneity of colorectal cancer and opened a new path in the analysis of colorectal cancer. For the same type of treatment, patients with diverse genetic backgrounds showed diverse outcomes narrating the impact of genetic background on the disease [5]. Since the immune system had a vital role in the development of different types of cancer [6], it was believed that the genetic impact was associated with immunity-related factors [7].

Immunological data like immune cell density, type, and its location in tumor samples predicted the existence of colorectal cancer patients better than the existing histopathological features [8]. The development of colorectal cancer and its metastasis was affected by the tumor microenvironment in which the Immune cells were the vital parts [9]. Dendritic cells and tumor-penetrating macrophages in colorectal cancer were associated with nearby monitoring T-cells and systemic T-cell responses to antigens connected with tumors affected the survival of patients [10].

Even though the immune-related genes and other tumor microenvironments have a handy role in the incidence and progress of colorectal cancer, at present there is no specific prognostic model on the basis of these tumor microenvironments to forecast the complete diagnosis of colorectal cancer patients and systemic assessment of these tumor microenvironment of colorectal cancer [11]. Hence, developing an immune-based prognostic model for the effective prediction of colorectal cancer prognosis has a vital clinical application. Tumor microenvironment (TME) genes that characterize the tumor cell surroundings are vital factors for the prognosis of colorectal cancer.

This proposal is focused on developing a comprehensive prognostic risk model by integrating TME gene expression profiles with molecular and medical data to increase the accuracy of prognostication for colorectal cancer.

The Objectives of the present research are:

* To detect a panel of TME genes linked with colorectal cancer prognosis using a complete literature review and bioinformatics study of freely accessible datasets.
* To integrate the TME gene expression profiles with medical and molecular characteristics of colorectal cancer patients for the construction of an all-inclusive prognostic risk model.
* To authenticate the proposed model's performance with individual colorectal cancer patient cohorts and to evaluate its clinical efficacy and predictive accuracy.
* To explore the biological importance of the recognized TME genes in colorectal cancer development and treatment response by functional enrichment analysis and experimental proof.

**Literature Review:**

Qian et al. (2021) [12] developed an innovative immune-related prognostic model as a self-determining prognostic indicator of colorectal cancer by indicating the penetration of immune cells and proving its vital role in the tumor microenvironment. They offered a different perception of the colorectal cancer immune microenvironment and treatment by conducting functional experiments on particular genes for confirmation of their clinical importance. As their study was a retrospective one, additional potential research is needed. The predictive ability of their model in colorectal cancer sought further testing for better prognostic categorization and treatment administration. There was a need for a complete study of the 18 immuno-related genes (IRGs) biological functions as many IRGs were related to the prognosis of colorectal cancer significantly. Their research has provided a deeper understanding of IRGs in colorectal cancer and given novel and budding diagnostic and clinical biomarkers [12].

Wang et. al. (2021) [13] generated the immunal score, one of the promising prognostic features using the ESTIMATE algorithm, and established a thirteen-gene model. The clinically significant model gave additional data for a better understanding of the tumor microenvironment. The results of the functional analysis provided an innovative perception for identifying the molecular mechanism at the beginning of the tumor and its development.

Yang et. al. (2021) [14] revealed that lipid metabolism-related genes (LMRG) had a prognostic effect in colorectal cancer and were involved in oppressive immune microenvironment formation. Lipid metabolism-related genes like CPT2, CCKBR, FDFT1, and PROCA1 were potential prognostic markers and therapeutic targets for colorectal cancer. This lipid metabolism-related prognostic model represented a potential biomarker for the prediction of chemotherapy efficacy and anti-PD-L1 therapy efficacy in colorectal cancer.

Song et al. (2021) [15] exposed a widespread regulatory mechanism that has an impact on the tumor-immune-stromal microenvironment, tumor diagnosis, and its clinicopathological features. They also highlighted the vital clinical implications of pyroptosis-related genes by estimating their therapeutic accountability in targeted therapy and immunotherapy. They also provided innovative ideas for guiding personalized immunotherapy approaches for colorectal cancer patients.

He et al. (2022) [16] identified molecular necroptosis subtypes in colorectal cancer patients and constructed a prognostic model on the basis of the genes that expressed differentially between the subtypes and the linkage between necroptosis with immune microenvironment and patient diagnosis. Though the NRS score obtained by this prognostic model predicted the patient’s enduring survival along with their therapeutical response to anti-PDL1 immunotherapy, this model has its limitations as their study sample was based on retrospective data. Larger potential data was needed to validate their findings and further *in vitro* and *in vivo* studies were required to explore the specific molecular mechanisms of the prognostic genes.

Zhou et. al. (2019) [17] developed a strong tool for survival prediction and treatment management in patients with stage I–III colorectal cancer based on the tumor microenvironment risk score (TMRS). The retrospective nature of the patient population used and the model construction based on the transcriptome profiling produced by GPL570 platform was a major drawback that sought further potential clinical trials. This made this model a suspected one while using for samples tested through platforms other than GPL570. Also, the optimal cut-off value has to be checked as the gene expression data was given as categorical variables in Cox regression.

Zhou et al. (2022) [18] predicted the overall survival in Colon adenocarcinoma (COAD) using an innovative risk score model on the basis of 33 genes. This model was significantly related to the hostile clinical outcome of the disease as it provided a more effective personalized therapeutic decision-making. High-risk Colon adenocarcinoma patients were identified using a nomogram model and consequently, their opt treatment plans were selected.

Wang et al. (2022) [19] developed a novel risk score model with outstanding insight and standardization for colorectal cancer prognosis employing eight transient receptor potential channel genes (TRPCG). This model was considered a hopeful biomarker for the detection of immune checkpoint inhibitors (ICIs) and neoadjuvant treatment in colorectal cancer diagnosis. For patients with locally advanced rectal cancer with low transient receptor potential channel (TRPC) scores, neoadjuvant chemoradiotherapy (NCRT) was suggested, and for those with high TRPC scores, a combination of MAPK inhibitors with neoadjuvant immunotherapy was suggested.

Zhang et al. (2024) [21] developed a classy risk model by leveraging machine learning and multi-omics perceptions, which precisely prognosticates the results for colorectal cancer patients. This model paved the way for more personalized and efficient oncologic treatment patterns. They also determined the molecular intricacies of colorectal cancer by extracting a reputed oppressive interaction among the lengthy non-coding RNA PVT1 and the EMT-related genes like MMP1 and TIMP1.

**Research Design and Methods:**

***a. Data Collection:***

Molecular and clinical data like demographic data, characteristics of tumors, treatment schedules, and survival outcomes will be collected from a group of colorectal cancer patients and reviewed. Gene expression datasets containing tumor microenvironment profiles of colorectal cancer samples will be collected from public repositories and analyzed.

***b. Identification of TME-Associated Genes:***

Systematic literature review and meta-analysis to recognize tumor microenvironment genes related with colorectal cancer prognosis will be identified using a systemic review of the literature and its meta-analysis. Bioinformatics analysis of gene expression data will be used to categorize the colorectal cancer tumor microenvironment genes depending on its functional significance and differential expression.

***c. Development of Prognostic Risk Model:***

The obtained tumor microenvironment gene expression profiles will be integrated with molecular and clinical data by employing cutting-edge statistical and machine-learning procedures. A strong prognostic risk model with the ability to segregate colorectal cancer patients into different risk groups based on feature selection and model optimization will be developed.

***d. Model Validation:***

The performance of this proposed model will be assessed by individual colorectal cancer patient cohorts, insight assessment, standardization, and clinical efficacy. Then the model will be compared with existing prognostic models to establish pre-eminence in stratification of risk and prognostic precision.

***e. Functional Analysis and Experimental Validation:***

The biological pathways linked with identified tumor microenvironment genes were illuminated using functional enhancement analysis. The key tumor microenvironment genes will be validated by experimentation using *in vitro* and *in vivo* models and their roles in colorectal cancer progression and treatment response will be confirmed.

**Expected Outcomes:**

* A comprehensive prognostic risk model integrating tumor microenvironment genes for precise prognosis of colorectal cancer in patients will be developed.
* Novel tumor microenvironmental genes related to colorectal cancer prognosis will be identified and their biological significance will be determined.
* A better understanding of the tumor microenvironment effect in colorectal cancer development and response to treatment will be achieved resulting in personalized therapeutic approaches.

**Implications and Contribution to Knowledge**

This research proposal will address the serious drawbacks in the existing prognostic models for colorectal cancer by integrating the different tumor microenvironment gene expression profiles. The complex relationship between tumor cells and their microenvironment was explained by the proposed model resulting in a momentous ability to improve prognostication accuracy and facilitate precise personalized treatment methods for colorectal cancer.

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