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Potential biomarkers for the prognosis of gastrointestinal stromal tumors

Potential biomarkers for GIST prognosis

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Abstract

In this editorial we comment on the article by Zhao JL *et al*. published in the recent issue of the World Journal of Gastrointestinal Oncology 2024. This study aims to explore the relationship between preoperative inflammation markers and the recurrence of gastrointestinal stromal tumors (GIST) after surgery. It is well known that the best-documented prognostic parameters for GIST are mitotic activity, tumor size and anatomical site. Besides, mutation status reprents a prognostic as well as predictive factor. This study provides a new tool for postoperative recurrence risk assessment of GIST patients by establishing a line chart prediction model, which is certificated by previous research that high platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) correlated with increased tumour sizes, more advanced tumour stages and mitotic index (PMID: 35117879). However, as a retrospective study, inevitable bias exists in the results; furthermore, the sample size of this study is relatively small, influencing the universality of the results. Moreover, when assessing risk rating and prognosis of GIST, some novel inflammatory makers could be taken into consideration, such as proenkephalin and SLITRK3. Overall, this study can offer an additional model for GIST prognosis and recurrence risk assessment, independent of the traditional prognostic factors of GIST.

Key Words: gastrointestinal stromal tumors; Recurrence Risk; Personalized Therapy

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Core Tip: he importance of predicting prognosis in the management of gastrointestinal stromal tumors (GISTs) is well known, with a particular focus on mitotic activity, tumor size, anatomical location, and KIT and PDGFRA mutation status. It underscores the emerging significance of inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), systemic immune-to-inflammation index (SII), platelet-to-lymphocyte ratio

(PLR), and monocyte-to-lymphocyte ratio (MLR) in predicting GIST prognosis and recurrence risk. This study identified the MLR and PLR as independent risk factors, thereby providing a predictive model for recurrence-free survival (RFS). However, it is important to note that the study has limitations, including its retrospective design, small sample size, and lack of external validation.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor with variable behavior, with an incidnce ranging from 1.1 to 1.5 cases per 100 000 person/years[1]. In contrast, microGIST are relatively common. Prognostic parameters play a crucial role in the management of gastrointestinal Stromal Tumors (GIST), helping to estimate the risk of recurrence after surgery, which is essential for establishing adjuvant therapy schemes.The best-documented prognostic parameters for GIST are mitotic activity, tumor size and anatomical site. Besides, mutation status of KIT and PDGFRA serves as a prognostic and predictive parameter[2, 3]. These elements are incorporated into the National Institutes of Health (NIH) risk classification system, which categorizes GIST cases into low-risk, intermediate-risk, and high-risk groups for recurrence[4,5]. This classification facilitates establish the strategy of adjuvant therapy, highlighting the importance of prognostic indicators. It is recommended that patients with high-risk GSIT may get privileged form a standard three-years adjuvant treatment. Many clinical trials have recommended imatinib as the first-line treatment for GIST, with sunitinib, regorafenib, and ripretinib identified as subsequent therapeutic options for advanced cases[3]. Additionally, various tyrosine kinase inhibitors are utilized in different treatment settings[6].

EXPANDING INFLAMMATORY INDICATORS FOR GIST

In recent years, inflammatory markers, such as the neutrophil/Lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet/Lymphocyte ratio (PLR), and monocyte/Lymphocyte ratio (MLR) , demonstrate potential value for prognostic

indication of various cancers, including GIST[7-10]. Compared to classical prognostic parameters, inflammatory markers are readily accessible and cost-effective, providing additional prognostic information that allows clinicians conduct more comprehensive assessments[8, 9]. In patients with GIST, inflammatory markers are proved be associated with disease recurrence risk. Not only do these markers reflect systemic anti-tumor inflammatory response but they are also closely associated with tumor progression, invasion, and prognosis. Elevated levels of certain markers may indicate a more aggressive disease phenotype and poorer prognosis in GIST. Besides, inflammatory markers are also explored to predict neoadjuvant and immunotherapy efficacy for advanced tumor patients[11, 12]. Additionally, in GIST, inflammatory markers also relate to angiogenesis and immuno-response within the tumor microenviroment. These markers provide insights into host's immune status, which can facilitate personalized treatment decisions. Furthermore, certain inflammatory markers may serve as predictors of adjuvant treatment efficacy, offering promising prognostic value for recurrence-free survival (RFS) in patients[3, 13-21] (Table 1).

However, these results may be influenced by various factors, including infections status, nutritional status, and other conditions unrelated to cancer. This could potentially result in false-positive outcomes during prognostic assessments. Therefore, ensuring the consistency and reproducibility of inflammatory markers is essential for their clinical application. Further validation of their prognostic value calls for larger, multicenter studies. Standardized thresholds should be established for these markers[3, 14]. It is of great significance to establish standardized thresholds and interpretations for these markers to enhance their reliability across different studies and clinical settings.

Regarding this study, which identified MLR and PLR as independent risk factors among four inflammatory biomarkers derived from neutrophils, platelets, monocytes, and lymphocytes (Figure 1), the authors established a line chart prediction model correlating inflammatory markers with RFS and offered a novel clinical tool for assessing postoperative recurrence risk in GIST patients. This study also emphasized

the ongoing sensitivity of inflammatory markers in patients receiving postoperative targeted therapy.

Nevertheless, as a relatively small sample retrospective study, inevitable bias exists in the results. Secondly, the study only conducted internal validation without external or multicenter data verification. Thirdly, the impact of postoperative targeted therapy on prognostic data may not fully reflect the operative situation. It is of great importance of a larger sample size, external validation of the prediction model, deeper exploration of novel biomarkers, better handling of confounding factors, and improved practical application of findings for this study. We suggest the authors to create a user-friendly online platform where clinicians can input patient data and obtain prognostic predictions based on the model and validate standardized thresholds for the inflammatory markers used in the model.

NOVEL PROGNOSTIC PARAMETERS FOR GIST

Research into novel prognostic parameters for GIST is thriving. New markers such as cytokines and chemokines are being explored for their potential role in GIST prognosis. Recent studies identified SLITRK3 as a significant predictor for the recurrence and metastasis of GIST, with higher expression levels correlating with poorer patient outcomes[18]. On the other hand, another study found that high proenkephalin (PENK) expression in GIST is associated with better overall survival and recurrence-free survival[19]. On the molecular front, next-generation sequencing of liquid biopsy detecting circulating tumor DNA (ctDNA) offers a non-invasive approach to detect mutation status and monitor progression and response to treatment in real-time[22].

CONCLUSION

In conclusion, integration both classical and novel prognostic parameters-including inflammatory markers-into the clinical management of GIST, is essential for personalized treatment strategies. These markers hold promising value for enhancing risk stratification, guiding adjuvant therapy decisions, and improving our ability to predict and manage disease recurrence among GIST patients. Further research is

warranted to fully elucidate the mechanisms underlying the association between inflammation and GIST progression and to translate these findings into clinical practice.

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