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The Role of Emerging Inflammatory Markers, YKL-40 and Pentraxin 3, in Predicting Prognostic Outcomes and Histopathological Grading of Colorectal Cancer: A Literature Review

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ABSTRACT

Colorectal cancer (CRC) progression is heavily influenced by localized inflammation within the tumor microenvironment. While traditional systemic markers often lack specificity, emerging biomarkers such as Pentraxin 3 (PTX3) and YKL-40 offer targeted insights into tumor aggressiveness and structural pathology. A literature review was conducted, encompassing in vitro assays, retrospective cohorts, and prospective analyses evaluating PTX3 and YKL-40 expression in colorectal malignancies. Elevated PTX3 levels drive an immunosuppressive state via M2-like macrophage polarization and correlate strongly with advanced TNM staging, deeper invasion, and poorer survival outcomes. Similarly, YKL-40 upregulation is specifically localized at the tumor's invasive front, strongly indicating tumor budding and cellular invasion. Clinically, high expression of both markers significantly predicts shorter overall survival, increased postoperative recurrence, and resistance to targeted treatments such as cetuximab and chemoradiotherapy. PTX3 and YKL-40 serve as robust prognostic and predictive biomarkers in CRC. Their strong correlation with adverse histopathological grading highlights their potential to out-perform traditional markers, ultimately refining clinical risk stratification and guiding personalized therapeutic interventions.

Keywords: Colorectal Cancer; Pentraxin 3; YKL-40; Prognostic Outcomes; Histopathological Grading; Tumor Budding; Biomarkers.
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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and remains a leading cause of cancer-related mortality, with more than 1.9 million new cases and approximately 930,000 deaths reported globally in 2020, and the burden is projected to increase substantially in the coming decades. Increasing evidence indicates that chronic inflammation contributes to CRC progression through modulation of the tumor microenvironment; however, conventional inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-8 (IL-8) have limited specificity, prompting growing interest in more tumor-associated markers such as Pentraxin 3 (PTX3) and YKL-40 for prognostic assessment.[1–3]

Pentraxin 3, a member of the long pentraxin superfamily, is synthesized locally by vascular endothelial cells, fibroblasts, and myeloid cells in response to inflammatory stimuli, contrasting with the hepatic production of short pentraxins like CRP. In CRC, PTX3 plays a multifaceted role in modulating the stroma; it has been shown to drive an immunosuppressive microenvironment by promoting M2-like macrophage polarization and activating complement cascades, which strongly correlates with advanced disease stages, tumor relapse, and poor survival outcomes.[4] Concurrently, YKL-40, a highly conserved glycoprotein secreted by both cancer cells and tumor-infiltrating macrophages, serves as a potent regulator of cellular migration, extracellular matrix remodeling, and angiogenesis. Elevated expression of YKL-40 in tissue and serum has been linked to epithelial-mesenchymal transition (EMT), targeted therapy resistance, and reduced overall survival in colorectal malignancies.[5,6]

Beyond systemic circulation, the clinical relevance of these biomarkers is closely tied to distinct histopathological features at the tumor invasive front. Histopathological grading, particularly the presence of "tumor budding", defined as isolated single cancer cells or small clusters of fewer than five cells at the invasive margin, is an established indicator of high-grade tumor aggressiveness. Recent evidence indicates that YKL-40 is highly overexpressed at the tumor-stroma interface, specifically within tumor buds and peritumoral immune cells, suggesting its direct involvement in driving cellular

detachment and local invasion.[7–9] Furthermore, the expression of these markers within the TME correlates with key immunoregulatory molecules such as PD-L1 and matrix metalloproteinases, driving an immunosuppressive niche that functions independently of systemic metabolic conditions.[10]

Given the growing need for precise prognostic tools that bridge systemic inflammation and localized histopathology, a collective evaluation of these emerging markers is warranted. While individual studies have explored the diagnostic or prognostic potential of either PTX3 or YKL-40, a comprehensive synthesis addressing their combined utility in relation to tumor grading and survival outcomes is still lacking.[11] Therefore, this review aims to systematically analyze the roles of YKL-40 and PTX3 in predicting prognostic outcomes and histopathological grading in colorectal cancer, providing a holistic perspective on their potential translation into personalized clinical oncology.

MATERIALS AND METHODS

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies investigating the emerging roles of Pentraxin 3 (PTX3) and YKL-40 (CHI3L1) in colorectal cancer (CRC). Electronic databases, including PubMed and Google Scholar, were systematically queried. The search strategy utilized a combination of specific keywords and Medical Subject Headings (MeSH) terms, including: ("Colorectal Cancer" OR "CRC" OR "Rectal Neoplasms") AND ("YKL-40" OR "CHI3L1" OR "Chitinase-3-like protein 1" OR "Pentraxin 3" OR "PTX3") AND ("Prognosis" OR "Survival" OR "Histopathological Grading" OR "Tumor Budding").

Selection Criteria

To ensure the clinical relevance and quality of the reviewed literature, specific inclusion and exclusion criteria were applied to screen the retrieved articles. Inclusion criteria includes, (1) Original research articles, including prospective cohorts, retrospective tissue/serum analyses, and in vitro/in vivo experimental models; (2) studies specifically evaluating the expression levels of YKL-40 and/or PTX3 in relation to CRC; and (3) studies reporting defined prognostic outcomes (e.g., overall survival, disease-free survival, relapse rates) and/or specific histopathological features (e.g., TNM staging, depth of invasion, tumor budding).

While (1) Purely descriptive reviews, case reports, and letters to the editor; (2) studies focusing on malignancies entirely unrelated to the colorectal or anal tract; and (3) articles lacking verifiable clinical data or full-text accessibility, are excluded.

Data Extraction and Synthesis

Following the initial electronic search and removal of duplicates, the titles and abstracts of retrieved records were screened for eligibility. Full-text reviews were subsequently performed for the remaining articles. Data extraction was systematically carried out to capture critical study variables, which included: first author, publication year, study design, sample size (human cohorts and experimental models), specific biomarkers evaluated, cutoff values, key histopathological correlations, and primary survival outcomes. Given the methodological heterogeneity among the included studies, particularly regarding detection techniques (enzyme-linked immunosorbent assay [ELISA], immunohistochemistry [IHC]) and biomarker cutoff thresholds, a narrative synthesis approach was adopted to evaluate the data, precluding a quantitative meta-analysis.

RESULTS AND DISCUSSION

Overview of Colorectal Cancer and Histological Grading

Colorectal cancer is one of the most common malignancies worldwide and remains a major contributor to cancer-related mortality despite advances in screening and therapeutic approaches. Globally, CRC ranks as the third most frequently diagnosed cancer and the second leading cause of cancer death, reflecting its substantial public health burden. The development of CRC is characterized by marked biological heterogeneity, resulting in variable tumor behavior, treatment response, and clinical outcomes. Therefore, understanding the underlying molecular and histopathological characteristics of CRC has become increasingly important to improve prognostic assessment and support individualized therapeutic strategies.[6]

The pathogenesis of CRC is a multistep process driven by the progressive accumulation of genetic, epigenetic, and inflammatory alterations that transform normal colonic epithelium into invasive carcinoma. Classical colorectal carcinogenesis predominantly follows the adenoma–carcinoma sequence, involving sequential mutations in genes such as APC, KRAS, and TP53, which lead to dysregulated cell proliferation, impaired apoptosis, and genomic instability. Alternative pathways, including microsatellite instability (MSI) and CpG island methylator phenotype (CIMP), also contribute to tumor initiation and progression. In addition, chronic inflammation has emerged as a critical mediator of colorectal carcinogenesis by promoting a tumor microenvironment characterized by immune dysregulation, angiogenesis, extracellular matrix remodeling, and enhanced metastatic potential.[6]

Histopathological grading remains an essential component in the evaluation of CRC because it reflects the degree of tumor differentiation and serves as an indicator of biological aggressiveness. Histologically, CRC is commonly classified into well-differentiated (low grade), moderately differentiated, and poorly differentiated (high grade) tumors based on glandular architecture, cellular atypia, and preservation of normal tissue organization. Higher histopathological grades are generally associated with increased proliferative activity, greater invasiveness, lymphovascular dissemination, and poorer survival outcomes. However, because tumors with similar histological features may demonstrate different clinical behaviors, there is increasing interest in integrating histopathological grading with inflammatory and molecular biomarkers, including emerging markers such as YKL-40 and Pentraxin 3, to improve prognostic stratification in CRC.[12]

Previous Studies related to the Role of YKL-40 and Pentraxin 3 in Predicting Prognostic Outcomes and Histopathological Grading of Colorectal Cancer

A total of 12 studies were included in this review, comprising retrospective cohorts, prospective analyses, and experimental models involving *in vitro* and *in vivo* assays. The evaluated studies focused on the diagnostic, prognostic, and histopathological significance of emerging inflammatory biomarkers, specifically Pentraxin 3 (PTX3) and YKL-40 (CHI3L1), predominantly in colorectal cancer (CRC) and related malignancies such as anal squamous cell carcinoma.

Pentraxin 3 (PTX3) Expression and Clinical Outcomes

Multiple studies consistently demonstrated that elevated serum or plasma levels of PTX3 are significantly associated with poor prognostic outcomes in CRC. Liu et al. (2018) reported that high preoperative serum PTX3 levels serve as an independent predictor of lower 5-year overall survival rates. Similarly, Zhang et al. (2016) identified that a plasma PTX3 cutoff of 12.0 ng/mL could predict tumor relapse with a sensitivity of 81.3% and a specificity of 69.5%. Furthermore, Wang and Wang highlighted that PTX3, when analyzed in combination with APE1-AAbs and miR-486-3p, provides highly robust predictive value (AUC: 0.875) for postoperative recurrence and metastasis.[12] At the histopathological level, elevated PTX3 is strongly associated with advanced TNM staging and greater invasion depth. Chen et al. (2024) elucidated the underlying microenvironmental mechanism, revealing that PTX3 promotes an immunosuppressive state by driving M2-like macrophage polarization, which subsequently inhibits cytotoxic CD8+ T cells. Additionally, increased PTX3 expression is positively correlated with inflammatory signatures and the activation of complement proteins (C3, C4, and C5b9).

YKL-40 Expression and Clinical Outcomes

The upregulation of systemic and tissue YKL-40 is a consistent indicator of adverse survival outcomes. Fuksiewicz et al. found that pretreatment serum YKL-40 levels >44.6 pg/mL independently predicted shorter disease-free and overall survival in patients with nonmetastatic rectal cancer.[5] De Robertis et al. confirmed these findings across broader CRC populations, noting that high YKL-40 correlates with poor overall survival, reduced disease-free survival, and resistance to targeted therapies such as cetuximab.[6] In a related context, Gambella et al. observed that a high serum YKL-40 level (>75 ng/mL) significantly increased the hazard ratio for mortality (HR: 2.82).[13] As a diagnostic adjunct, Safiejko et al. reported that YKL-40 offers an AUC of 0.702 with a high specificity of 77.5%, making it a valuable complement to conventional CEA testing.[14]

YKL-40 expression is intimately linked to aggressive histopathological features, most notably at the tumor invasive front. Kazakova et al. identified strong YKL-40 immunoreactivity specifically within tumor buds in 96.8% of cases, directly contrasting with the low expression observed in the main tumor parenchyma.[8] This distinct spatial distribution at the invasive margin was corroborated by Ivanova et al., reinforcing the critical role of YKL-40 in facilitating tumor budding and cellular invasion.[9]

Beyond Traditional Biomarkers: The Pathophysiological Role of PTX3 and YKL-40

Traditional systemic inflammatory markers, such as C-Reactive Protein (CRP) and Interleukin-8 (IL-8), have long been utilized to assess systemic inflammation. However, they generally lack specificity regarding the localized tumor microenvironment (TME). This review highlights a critical paradigm shift toward emerging biomarkers, notably Pentraxin 3 (PTX3) and YKL-40 (CHI3L1), which are not merely bystanders but active participants in tumorigenesis. Unlike hepatic-derived CRP, PTX3 is produced locally by stromal and inflammatory cells in response to primary oncogenic signals. Chen et al. established that PTX3 actively drives an immunosuppressive TME by promoting M2-like macrophage polarization, which subsequently suppresses cytotoxic CD8+ T cell activity.[3] Similarly, YKL-40 expression contributes to this immunosuppressive state by upregulating MMP-8, IL-17A, and PD-L1 within the tumor stroma, functioning entirely independently of systemic metabolic comorbidities such as obesity or diabetes.[10]

Correlation with Histopathological Grading and the Invasive Margin

A critical aspect of evaluating colorectal cancer (CRC) prognosis is histopathological grading, particularly the microscopic evaluation of the invasive margin. Both PTX3 and YKL-40 demonstrate profound correlations with adverse histopathological features. Elevated serum PTX3 is significantly associated with advanced TNM staging and deeper tumor invasion (Liu et al., 2018). Furthermore, spatial analysis of YKL-40 reveals highly specific localization at the tumor's invasive front. Kazakova et al. reported strong YKL-40 immunoreactivity specifically within tumor buds in 96.8% of cases, distinguishing it from the characteristically low expression found in the main tumor parenchyma.[8] This precise localization at the invasive margin facilitates tumor budding and cellular invasion, a finding strongly corroborated by Ivanova et al..[9] Functionally, the upregulation of YKL-40 drives the epithelial-mesenchymal transition (EMT) by altering the expression of E-cadherin and Vimentin, thereby promoting a highly aggressive metastatic phenotype.[6]

Prognostic Significance and Predictive Utility in Clinical Practice

The integration of PTX3 and YKL-40 into clinical assessments offers substantial prognostic value that outperforms or complements conventional markers. High pretreatment serum YKL-40 levels independently predict shorter disease-free and overall survival in both metastatic and nonmetastatic CRC cohorts.[5,13] Interestingly, the cellular origin of YKL-40 expression significantly influences its prognostic weight; Oh et al. identified that YKL-40 expression specifically within infiltrating immune cells, rather than the tumor cells themselves, serves as an independent poor prognostic factor, particularly in stage III CRC.[7] In terms of predicting tumor recurrence, Zhang et al. demonstrated that a plasma PTX3

Table 1. Summary of Studies related to the Role of YKL-40 and Pentraxin 3 in Predicting Prognostic Outcomes and Histopathological Grading of Colorectal Cancer

Study	Study Design	Biomarkers Evaluated	Key Findings
Chen et al., 2024[3]	In vitro assays, in vivo loss-of-function assays (knockout mice), and bioinformatic analyses.	PTX3.	PTX3 expression positively correlates with inflammatory signatures and poor survival in colon cancer patients. Blockade of PTX3 reduces M2 macrophages and increases cytotoxic CD8+ T cells.
De Robertis et al., 2022[6]	In vitro experiments, in vivo murine model, public dataset analysis (TCGA, GEO), and retrospective tissue/serum analysis.	YKL-40 (CHI3L1), EMT-related genes (N-cadherin, Vimentin, E-cadherin, etc.).	Serum and tissue YKL-40 levels are significantly elevated in CRC compared to controls. High YKL-40 correlates with poor overall survival, disease-free survival, and resistance to cetuximab therapies.
Fuksiewicz et al., 2018[5]	Retrospective serum analysis via enzyme-linked immunosorbent assay (ELISA).	YKL-40, Carcinoembryonic Antigen (CEA).	Pretreatment serum YKL-40 was elevated in 54% of rectal cancer patients compared to 35% for CEA. High YKL-40 levels (>44.6 pg/mL) were significantly associated with shorter disease-free and overall survival.
Gambella et al., 2024[13]	Retrospective multi-institutional cohort study involving immunohistochemistry (IHC) and enzyme immunoassay.	YKL-40 (serum and tissue protein), p16.	High serum YKL-40 (≥ 75 ng/mL) significantly associated with older age, comorbidities, and a worse 5-year survival rate (HR: 2.82). High YKL-40 expression in peritumor immune cells correlated significantly with a lack of response to chemoradiotherapy.
Ivanova et al., 2026[9]	Prospective analysis using IHC, ELISA, and qRT-PCR on patient blood and tissue samples.	YKL-40 (CHI3L1), YKL-39 (CHI3L2).	Plasma YKL-40 levels were significantly higher in CRC patients, while YKL-39 levels were significantly lower compared to controls. Both chitinase-like proteins showed strong tissue expression at the tumor invasive front, specifically within tumor buds.
Kazakova et al., 2024[8]	Retrospective tissue review employing IHC.	YKL-40.	Strong YKL-40 immunoreactivity was identified at the tumor front (tumor buds) in 96.8% of cases, contrasting with low expression in the tumor parenchyma (19.6%).
Liu et al., 2018[2]	Retrospective cohort study using ELISA.	PTX3.	Serum PTX3 levels were significantly higher in CRC patients than in healthy volunteers. Elevated PTX3 levels were strongly associated with advanced TNM stage, invasion depth, and lower 5-year overall survival.
Ochman et al., 2023[10]	In silico analysis (GEO, TCGA datasets) combined with ex vivo tissue homogenate analysis via ELISA.	YKL-40, MMP-8, IL-17A, PD-L1.	YKL-40 expression was significantly elevated in tumor tissues compared to margins and positively correlated with MMP-8, IL-17A, and PD-L1 levels. YKL-40 levels showed no significant association with diabetes, obesity, or smoking.
Oh et al., 2021[7]	Retrospective tissue microarray study utilizing IHC.	YKL-40, PD-L1, CD3, CD8.	YKL-40 expression in immune cells (but not tumor cells) significantly correlated with worse overall survival (p=0.047). Immune cell YKL-40 expression was an independent poor prognostic factor particularly in stage III and high-immunoscore subgroups.
Safiejko et al., 2025[14]	Prospective diagnostic performance analysis using multiplexing assays and chemiluminescent microparticle immunoassay (CMIA).	YKL-40, RLN2, CEA, CA 19-9.	Serum YKL-40, CEA, and CA 19-9 were significantly higher in CRC patients versus controls, but RLN2 was not. YKL-40 demonstrated moderate sensitivity (65%), high specificity (77.5%), and an AUC of 0.702.
Wang & Wang, 2025[12]	Retrospective observational study.	APE1-AAbs, PTX-3, miR-486-3p.	Levels of APE1-AAbs, PTX-3, and miR-486-3p were significantly elevated in patients experiencing recurrence and metastasis. The combination of all three markers provided the highest predictive value (AUC: 0.875).
Zhang et al., 2016[1]	Prospective comparative study analyzing plasma samples.	PTX3, Complement proteins (C3, C4, C5b9).	Plasma PTX3 levels were significantly higher in CRC patients. A PTX3 cutoff of 12.0 ng/mL predicted tumor relapse with 81.3% sensitivity and 69.5% specificity. PTX3 levels positively correlated with C3, C4, and C5b9 levels.

*abbreviations: APE1-AAbs: Apurinic/Apyrimidinic Endonuclease 1 Autoantibodies; ASC: Anal Squamous Cell Carcinoma; AUC: Area Under the Curve; CA 19-9: Carbohydrate Antigen 19-9; CD3 / CD8: Cluster of Differentiation 3 / Cluster of Differentiation 8 (T-cell surface markers); CEA: Carcinoembryonic Antigen; CHI3L1: Chitinase-3-like 1 (also known as YKL-40); CHI3L2: Chitinase-3-like 2 (also known as YKL-39); CMIA: Chemiluminescent Microparticle Immunoassay; CRC: Colorectal Cancer; ELISA: Enzyme-Linked Immunosorbent Assay; EMT: Epithelial-Mesenchymal Transition; GEO: Gene Expression Omnibus (a public functional genomics data repository); HR: Hazard Ratio; IHC: Immunohistochemistry; IL-17A: Interleukin-17A; miR-486-3p: MicroRNA 486-3p; MMP-8: Matrix Metalloproteinase-8; PD-L1: Programmed Death-Ligand 1; PTX3: Pentraxin 3; qRT-PCR: Quantitative Reverse Transcription Polymerase Chain Reaction; RLN2: Relaxin-2; TCGA: The Cancer Genome Atlas; TILs: Tumor-Infiltrating Lymphocytes; TME: Tumor Microenvironment; TNM: Tumor, Node, Metastasis (cancer staging system).

cutoff of 12.0 ng/mL effectively predicts CRC relapse, which is also linked to the activation of complement proteins.[1] The predictive accuracy can be further optimized using a multi-marker approach. For instance, combining PTX3 with APE1-AAbs and miR-486-3p yields an exceptionally high predictive value (AUC: 0.875) for postoperative metastasis.[12] As a diagnostic adjunct, YKL-40 provides high specificity and successfully complements conventional tumor markers like CEA.[14] Moreover, elevated YKL-40 levels strongly correlate with resistance to targeted treatments, including cetuximab and chemoradiotherapy, highlighting its indispensable potential in guiding personalized oncological therapeutic strategies.[6,13]

While the clinical utility of PTX3 and YKL-40 is firmly supported by current literature, certain limitations must be addressed. The heterogeneity in detection methodologies (e.g., ELISA, IHC, CMIA) and the lack of universally standardized cut-off values for "elevated" markers across different clinical laboratories pose challenges for immediate, widespread clinical implementation. Future prospective, large-scale multicenter studies are required to establish standardized reference intervals and further elucidate the longitudinal dynamics of these biomarkers in response to neoadjuvant therapies.[15–18]

CONCLUSION

In conclusion, this review underscores the critical role of Pentraxin 3 (PTX3) and YKL-40 as robust, emerging systemic inflammatory biomarkers in colorectal cancer (CRC), offering significant advantages over traditional markers like CRP and IL-8. Both PTX3 and YKL-40 are intimately involved in the modulation of the tumor microenvironment (TME) and the promotion of an immunosuppressive state. Crucially, these novel biomarkers demonstrate a profound correlation with aggressive histopathological grading. The distinct spatial upregulation of YKL-40 at the tumor's invasive front is a key indicator of tumor budding and cellular invasion, while elevated PTX3 levels are directly linked to advanced TNM staging and greater invasion depth.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest about this article.

AUTHOR CONTRIBUTION

IGBBAR and MAKA initiated the study concept and developed the review methodology. IGBBAR, MAKA, AAGCW, and IGAPS performed the literature identification, article selection, and data synthesis. IGPS provided scientific supervision, contributed to manuscript refinement, and ensured the overall quality and consistency of the review. All authors contributed to manuscript preparation, critically reviewed the final version, and approved the manuscript for publication.

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ETHICS APPROVAL

Not Applicable.

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