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ORIGINAL RESEARCH

CXCL11: A Novel Biomarker in Colorectal Cancer as Metastasis Predictor

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Objective: CXCL11 (C-X-C motif chemokine ligand 11) encodes a chemokine, a small signaling protein involved in immune and inflammatory responses. This study aims to evaluate the association between CXCL11 gene expression variations and metastasis in colorectal cancer (CRC) patients, highlighting its potential as a biomarker for metastasis.

Methods: This is observational laboratory-based study utilized tissue samples from colorectal cancer (CRC) patients stored in the Tissue Bank of the Research Unit, Division of Digestive Surgery, Faculty of Medicine, Universitas Padjadjaran. Conducted between January and August 2024, data collection involved pathological and anatomical assessments of tissue samples obtained through biopsies or tumor resections. Gene expression analysis was performed on 60 fresh tumor tissues using PCR at the Biomolecular Laboratory, Faculty of Medicine, Universitas Padjadjaran.

Results: The findings revealed a significant variation in CXCL11 expression among CRC patients based on cancer stage (P = 0.015) and metastasis status (P = 0.017). However, no significant differences in CXCL11 expression were observed concerning age, gender, anatomical pathology, or tumor location.

Conclusion: This study identifies a relationship between CXCL11 gene expression differences and metastasis in CRC patients. Further studies with larger sample sizes are recommended to validate CXCL11's role as a biomarker for CRC metastasis. Additionally, future research should explore the potential application of CXCL11 in antitumor therapy.

Plain Language Summary: Colorectal cancer (CRC) is one of the most common types of cancer worldwide, with two million new cases diagnosed each year. Early detection can improve survival rates and reduce complications. Scientists are exploring biomarkers—biological indicators in the body—that can help predict cancer progression and guide treatment decisions. This study investigates whether a specific gene, called CXCL11, is linked to the spread of colorectal cancer (metastasis). CXCL11 is involved in immune responses and inflammation, and it may influence cancer growth and spread. The researchers aimed to determine if measuring CXCL11 levels could help identify patients at higher risk of metastasis. The study analyzed tissue samples collected from colorectal cancer patients between between January and August 2024. These samples were stored in a tissue bank at Universitas Padjadjaran. Researchers used Polymerase Chain Reaction (PCR) to measure CXCL11 gene activity. Patients who had received chemotherapy or radiation therapy were excluded to ensure accurate results. The average age of patients was 54 years, about 45% of the patients had cancer that had spread (metastasis). CXCL11 levels were significantly higher in patients with advanced stages of cancer and those with metastasis. No significant differences in CXCL11 levels were found based on age, gender, tumor location, or cell type. This study suggests that CXCL11 could be a useful biomarker for predicting metastasis in colorectal cancer patients. Higher levels of CXCL11 were associated with advanced cancer stages and metastasis. Further research with larger groups of patients is needed to confirm these findings. Scientists may also investigate whether CXCL11 can be targeted in new treatments for colorectal cancer. Identifying biomarkers like CXCL11 can help doctors detect cancer earlier, predict its progression, and create personalized treatment plans. This could improve survival rates and quality of life for colorectal cancer patients.

Keywords: biomarker, cancer stage, colorectal cancer, CXCL11, metastasis

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Introduction

Colorectal cancer (CRC) has the third-highest incidence in the world and the fourth-highest in Indonesia among all types of cancer, with two million cases diagnosed each year.[1] The global death toll from CRC reached 900,000 in 2018.[2] In Indonesia, CRC has the fourth highest incidence among all types of cancer with 35,000 new cases and a death toll of 18,000 each year, which is the fourth leading cause of death among other cancers.[1,2] Early detection plays an important role in increasing survival and decreasing morbidity and mortality rates in CRC patients. Patients with risk factors will undergo physical examinations, blood tests, colonoscopy, Computed Tomography Colonography, and tumor marker examinations.[3]

Chemokines are signaling molecules that play a role in attracting and directing the movement of cells in the immune and inflammatory systems. Chemokine expression in CRC may play an important role in regulating the immune response, tumor progression/invasion, tumor microenvironment, and metastasis. Some chemokines that are frequently associated with colorectal cancer include CXCL10 (C-X-C motif chemokine ligand 10), CXCL11 (C-X-C motif chemokine ligand 11), and CXCL21 (C-C motif chemokine ligand 21). These are genes that encode chemokines, which are small signaling proteins involved in the immune and inflammatory responses.[4–7] Studies have been conducted to examine the role of expression of certain chemokine genes in the diagnosis, progression, and prognosis of CRC. Several studies have identified differences in the expression profiles of certain chemokine genes between normal colon tissue and CRC. The expression of these chemokine genes can be examined using NanoString technology and PCR.[5,8–11]

Specifically, the chemokine CXCL11 can also provide signals to attract immune cells to the tumor site. The chemokine CXCL11 is also involved in the development of various types of cancer, including CRC. Increased CXCL11 expression in CRC may contribute to the recruitment of immune cells and potentially modulate the immune response to the tumor.[12] Therefore, the researchers in this study aimed to assess the relationship between CXCL11 gene expression and metastasis in colorectal cancer patients.

Materials and Methods

Study Setting

This observational study utilized tissue samples from colorectal cancer patients stored in the Digestive Surgery Division Research Unit Tissue Bank, Faculty of Medicine, Universitas Padjadjaran. The samples were collected from patients treated at Dr. Hasan Sadikin General Hospital, Bandung, between January and August 2024.

Inclusion and Exclusion Criteria

Eligible participants included patients diagnosed with colorectal cancer based on pathological anatomy, aged 18 years or older, who provided informed consent. Patients who had undergone chemotherapy or radiation therapy were excluded. The sample size was determined to investigate the association between CXCL11 gene expression and metastasis in colorectal cancer patients.

Data Collection

Data collection involved direct pathological examinations of tissue samples obtained through biopsies or tumor resection surgeries. Gene expression analysis was conducted using fresh tumor tissues, processed in the Biomolecular Laboratory, Faculty of Medicine, Universitas Padjadjaran. DNA for CXCL11 analysis was either extracted from stored biological samples or isolated from fresh tissue preserved in RNAlater® solution (Qiagen). DNA extraction followed the Quick-DNA kit protocol (Zymo Research), and samples were stored at −20°C in the AIRA® tissue bank. DNA concentration and purity were measured using a Nanodrop 2000TM spectrophotometer (Thermo Fisher Scientific) with OD ratios of 230/260 and 280/260. For CXCL11 analysis, the qt-PCR-HRM Kit method was employed. The target locus was amplified using qt-PCR with 1000 ng of DNA, diluted to 20 ng/μL with nuclease-free water. MSI analysis was performed using RT-PCR HRM. Amplification cycles continued until the Cycle Threshold (CT) value was ≤37. Before testing, reagents were melted, spun, and vortexed, while controls were melted and spun. Reaction mixtures included 8 μL of the master mix and 2 μL of DNA template, prepared under light-protected conditions. Each test was performed in duplicate. The high-resolution qtPCR melting procedure involved three stages: heat activation (40 cycles), final extension, pre-melt,

and HRM analysis. The steps included 10 seconds of denaturation at 95°C, 30 seconds of annealing at 55°C, and 20 seconds of elongation at 72°C. This was followed by a 2-minute final extension at 72°C, two pre-melt phases at 95°C for 15 seconds and 60°C for 5 seconds, and HRM from 60°C to 90°C with increments of 0.3°C/1%. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as the housekeeping gene, acting as a reference for gene expression comparisons. The expression of CXCL11 is calculated as the average CT of CXCL11 minus the average CT of GAPDH and is expressed in delta CT units (ΔCT). A lower ΔCT value indicates high expression of CXCL11, while a higher ΔCT value indicates low expression of CXCL11.

Data Analysis

The variables in this study include histopathological type, CXCL11 gene expression, age, gender, and stage. Numerical data will be expressed as the mean, standard deviation, and median, while categorical data will be expressed as proportions (%). As the data were not normally distributed, the relationship between CXCL11 expression and clinicopathological characteristics was analyzed using the Mann–Whitney *U*-Test and the Kruskal–Wallis *H*-Test. The Mann–Whitney *U*-Test is used for comparing two independent groups, whereas the Kruskal–Wallis *H*-Test is used when comparing more than two independent groups. Data analysis was performed with SPSS version 26.

Results

A total of 60 subjects were included in this study based on predefined inclusion and exclusion criteria. The demographic and clinicopathological characteristics of the subjects are summarized in Table 1. The median age of participants was 54.50 years (range: 23–80 years). The study included 26 males (43.3%) and 34 females (56.7%). Based on anatomical pathology findings, adenocarcinoma was the predominant histological type (90%), followed by mucinous adenocarcinoma (8.3%) and signet ring cell carcinoma (1.7%). The rectum was the most common tumor site, found in 66.7% of patients, while 33.3% had tumors in the colon. In terms of cancer staging, 45% of patients were classified as stage IV, while 26.7%, 16.7%, and 11.7% were in stages III, II, and I, respectively. Metastases were observed in 27 patients (45%), while 33 patients (55%) had no evidence of metastasis.

Table 1 Research Subject Characteristics

Variable		Proportion (%)
Age	Mean Median (min-max) Minimum Maximum	54.25 ± 13.86 years 54.50 (23–80) 23 years 80 years
Sex	Male Female	26 (43.3%) 34 (56.7%)
Anatomical pathology Examination results	Adenocarcinoma Mucinous adenocarcinoma Signet ring cell	54 (90%) 5 (8.3%) 1 (1.7%)
Tumor site	Caecum Ascending Transverse Sigmoid Rectum	1 (1.7%) 2 (3.3%) 1 (1.7%) 16 (26.7%) 40 (66.7%)
Tumor location	Colon Rectum	20 (33.3%) 40 (66.7%)

(*Continued*)

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Table 1 (Continued).

Variable		Proportion (%)
Stage	I II III IV	7 (11.7%) 10 (16.7%) 16 (26.7%) 27 (45%)
Metastases	No metastases Metastases	33 (55%) 27 (45%)
CXCL11 expression level (ΔCT)	Mean Median (min-max) Minimum Maximum	8 ± 2.89 8.53 (0.10–13.01) 0.09 13.01

Table 2 Mean Difference in CXCL 11 Expression Level in Colorectal Cancer Patients

Variable		Mean ±SD (ΔCT)	Median (min-max)	Range	p-value
Age	Early onset (<50 years) Late onset	8.27 ± 2.64 7.73 ± 3.15	8.90 (1.41–11.60) 8.45 (0.10–13.01)	10.19 12.92	0.506a
Sex	Male Female	8.2 ± 3 7.84 ± 2.84	8.66 (0.10–13.01) 8.52 (1.28–11.42)	12.92 10.14	0.687a
Anatomical pathology	Adenocarcinoma Mucinous Adenocarcinoma Signet ring cell	7.95 ± 2.95 9.07 ± 2.1 4.94	8.48 (0.10–13.01) 9.59 (5.63–11.34) 4.94 (4.94–4.94)	12.92 5.71 0	0.384a
Tumor location	Colon Rectum	7.93 ± 3 8.03 ± 2.88	8.39 (0.10–11.42) 8.78 (1.28–13.01)	11.32 11.73	0.888a
Stage	I II III IV	7.85 ± 2.27 5.6 ± 4.29 7.92 ± 2.6 8.97 ± 2.09	8.45 (2.91–9/71) 5.22 (0.10–11.60) 8.38 (2.84–11.14) 9.15 (4.38–13.01)	6.8 11.5 8.3 8.63	**0.015b**
Metastasis	No metastasis Metastasis	7.2 ± 3.23 8.97 ± 2.09	8.32 (0.10–11.60) 9.15 (4.38–13.01	11.5 8.63	**0.017a**

Notes: a=Mann Whitney Test, b=Kruskal Wallis, bolded values indicate statistical significance ($p < 0.05$).

The median CXCL11 expression level was 8.53 ΔCT (range: 0.10–13.01 ΔCT). Table 2 presents the differences in CXCL11 expression based on clinicopathological features. Statistical analysis revealed a significant association between CXCL11 expression levels and cancer stage ($p = 0.015$) as well as metastasis status ($p = 0.017$). Patients with stage IV colorectal cancer had the highest CXCL11 expression levels with a median of 9.15 ΔCT (range: 4.38–13.01 ΔCT), while those with stage II disease had the lowest levels, with a median of 5.22 ΔCT (range: 0.10–11.60 ΔCT). Additionally, patients with metastatic disease had significantly higher CXCL11 expression (median: 9.15 ΔCT, range: 4.38–13.01 ΔCT) compared to those without metastases (median: 8.32 ΔCT, range: 0.10–11.60 ΔCT, $p = 0.017$).

Other factors, including age, sex, tumor location, and histological type, did not show a statistically significant correlation with CXCL11 expression. Although mucinous adenocarcinoma cases had a slightly higher CXCL11 expression (median: 9.59 ΔCT, range: 5.63–11.34 ΔCT) compared to adenocarcinoma cases (median: 8.48 ΔCT, range:

0.10–13.01 ΔCT), the difference was not statistically significant (p = 0.384). Similarly, no significant differences were observed between tumors located in the colon (median: 8.39 ΔCT, range: 0.10–11.42 ΔCT) and those in the rectum (median: 8.78 ΔCT, range: 1.28–13.01 ΔCT, p = 0.888) or between male (median: 8.66 ΔCT, range: 0.10–13.01 ΔCT) and female patients (median: 8.52 ΔCT, range: 1.28–11.42 ΔCT, p = 0.687). These findings suggest that CXCL11 expression is significantly associated with colorectal cancer progression, particularly in relation to tumor stage and metastatic status, while other factors, such as age, sex, tumor location, and histological type, do not significantly influence CXCL11 expression levels.

Discussion

In this study, the median age of participants was 54 years, with a higher proportion of women (34 samples) compared to men (26 samples). Histologically, most colorectal cancer (CRC) cases are carcinomas, with over 90% classified as adenocarcinomas. Less common types include adenosquamous, spindle cell, squamous cell, and undifferentiated carcinomas.[13,14] In this study, adenocarcinoma was the predominant histopathological finding among the subjects.

This study also revealed a significant difference in the location of colorectal cancer, with twice as many cases in the rectum as in the colon. Tumor staging was assessed using the TNM classification system established by the American Joint Committee on Cancer (AJCC).[15] Most subjects in this study were classified as stage IV, with a higher proportion of non-metastatic cases compared to those with metastasis.

The C-X-C motif chemokine ligand 11 (CXCL11), also known as IFN-inducible T cell α chemoattractant (I-TAC), facilitates the recruitment of T cells, natural killer (NK) cells, and monocytes/macrophages to infection sites. It primarily interacts with G protein-coupled receptors such as CXCR3, along with other chemokines like CXCL9 and CXCL10.[16] CXCL11 promotes cell proliferation and migration through receptor binding, playing a key role in directional cell movement. Additionally, it contributes to inflammation and its progression.[17]

Research by Tokunaga et al highlighted the role of CXCL11 in regulating oncogenic processes across various human cancers, including colorectal cancer. Elevated CXCL11 levels have been linked to advanced TNM stages in pancreatic cancer, promoting increased proliferation and metastasis.[18] Data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) showed higher CXCL11 expression in colon cancer tissues compared to normal tissues, with elevated CXCL11 levels associated with improved survival outcomes.[19] Similarly, this study found a significant association between CXCL11 gene expression levels and different stages of colorectal cancer.

This study identified a significant association between CXCL11 expression levels and colorectal cancer stage (p = 0.015), suggesting its potential role in tumor progression and immune response regulation. The median CXCL11 ΔCT values varied across different stages, with the highest ΔCT observed in stage IV patients (9.15 ΔCT, range: 4.38–13.01), followed by stage III (8.38 ΔCT, range: 2.84–11.14), stage I (8.45 ΔCT, range: 2.91–9.71), and the lowest in stage II (5.22 ΔCT, range: 0.10–11.60). Since a higher ΔCT value indicates lower CXCL11 expression, these results suggest that CXCL11 expression is lower in advanced stages of colorectal cancer.

These findings contrast with previous studies, such as those by Gao et al, which reported that higher CXCL11 expression was associated with more aggressive tumor features, including deeper invasion, increased lymph node involvement, and higher TNM stages.[20] The lower expression of CXCL11 observed in stage IV patients in this study suggests a possible immune evasion mechanism, where reduced CXCL11 expression may limit the recruitment of immune cells, such as T cells and macrophages, to the tumor site, thereby facilitating metastasis. Conversely, the higher CXCL11 expression (lower ΔCT values) observed in earlier stages may reflect an active immune response attempting to suppress tumor progression. Interestingly, stage II patients exhibited the lowest ΔCT values (5.22 ΔCT), indicating the highest CXCL11 expression, which deviates from the trend observed in other stages. This could suggest that CXCL11 plays a dual role depending on disease progression, with higher expression in early stages potentially promoting immune cell infiltration, while reduced expression in later stages may contribute to tumor immune escape.[21–23]

Distant metastasis is a crucial factor influencing the prognosis and treatment strategies for colorectal cancer, as it marks the transition from localized disease to systemic spread. In this study, a significant association was observed between CXCL11 expression and distant metastasis (p = 0.017), with metastatic patients exhibiting a higher median ΔCT value (9.15 ΔCT, range: 4.38–13.01) compared to non-metastatic patients (8.32 ΔCT, range: 0.10–11.60). Since higher

ΔCT values indicate lower CXCL11 expression, this result suggests that CXCL11 expression is significantly reduced in patients with distant metastasis. This finding highlights the potential role of CXCL11 in immune surveillance and tumor suppression during the early stages of CRC, while its downregulation in metastatic disease may contribute to immune escape and cancer progression.

Several mechanisms could explain the observed reduction in CXCL11 expression in metastatic CRC. One possible explanation is the shift toward an immunosuppressive tumor microenvironment as the disease progresses. Advanced tumors may actively suppress CXCL11 expression to limit the recruitment of immune cells such as cytotoxic T lymphocytes and natural killer cells, both of which play a crucial role in anti-tumor immunity. By reducing CXCL11-mediated chemotaxis, tumor cells may evade immune detection, allowing them to spread beyond the primary site. Another plausible mechanism involves tumor adaptation, where cancer cells selectively downregulate chemokines like CXCL11 to escape immune surveillance, particularly by decreasing infiltration of CXCR3-expressing CD8+ T cells and natural killer cells. This process may create a permissive microenvironment that facilitates distant metastasis. Additionally, the loss of CXCL11 expression could indicate a disruption in normal chemotactic signaling, further enabling tumor cells to escape immune-mediated destruction.[22–25]

The findings in this study contrast with some previous reports, such as those by Gao et al, which suggested that higher CXCL11 expression is associated with increased tumor progression. However, discrepancies between studies may arise due to differences in patient cohorts, molecular subtypes of CRC, and the immune landscape of tumors. Some CRC subtypes may exhibit high CXCL11 expression as part of an inflammatory response, while others may show its downregulation as a tumor adaptation strategy.[26] Differences in sample collection, gene expression quantification methods, and the specific immune composition of tumors could also contribute to these variations. The inverse association observed in this study supports the hypothesis that CXCL11 downregulation in metastatic CRC may be linked to immune suppression and tumor escape mechanisms, emphasizing the need for further research to determine whether restoring CXCL11 expression could enhance immune response and improve patient outcomes.

From a clinical perspective, the observed decline in CXCL11 expression in metastatic CRC raises important questions regarding its potential role as a biomarker for predicting metastatic potential. If confirmed in larger studies, CXCL11 downregulation could serve as an early indicator of disease progression, helping stratify patients based on their risk of developing distant metastases. Furthermore, given CXCL11's role in immune cell recruitment, its modulation could offer a novel therapeutic strategy to enhance the efficacy of immunotherapy. The integration of CXCL11 expression analysis with immune checkpoint inhibitors could provide valuable insights into patient responsiveness to treatment and open new avenues for personalized immunotherapy approaches in CRC.

Limitations and Future Directions

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of the findings. A larger cohort would allow for more robust conclusions and better stratification of patients based on clinicopathological characteristics. Second, the lack of normal or healthy subject samples as a control group prevents the establishment of a definitive cut-off point for CXCL11 expression in colorectal cancer. Without a baseline reference, it is difficult to determine whether CXCL11 expression in tumor tissues is upregulated or downregulated relative to normal conditions, which could provide crucial insights into its role in colorectal carcinogenesis. Future studies incorporating healthy controls or adjacent normal tissues would help establish clinically relevant expression thresholds. Third, our study population has selection bias, as the research was conducted primarily on patients from a tertiary referral hospital, where advanced-stage cases are more commonly treated. This may have resulted in a higher proportion of late-stage colorectal cancer cases, potentially skewing the observed associations between CXCL11 expression and disease progression. Future studies including patients from primary care or community hospital settings may help achieve a more representative sample of the general CRC population. Fourth, while we observed a decline in CXCL11 expression in advanced colorectal cancer stages, the underlying mechanisms remain unclear. It is uncertain whether this downregulation is a result of tumor-mediated immune suppression, a shift in the tumor microenvironment, or a response to tumor progression. Investigating the functional consequences of CXCL11 downregulation in later stages—such as its impact on immune infiltration, angiogenesis, or tumor growth—could help

elucidate its precise role in immune evasion and metastasis. Fifth, this study does not explore potential correlations between CXCL11 expression and other immune checkpoint markers, such as PD-1, PD-L1, or CTLA-4. Understanding these interactions could provide deeper insights into the immune landscape of colorectal cancer and determine whether CXCL11 expression modulates the effectiveness of immunotherapy strategies. Future research should investigate whether CXCL11 could serve as a predictive biomarker for immune checkpoint inhibitor response or as a therapeutic target in combination with immunotherapy. Fifth, this study does not explore alternative techniques for CXCL11 examination or potential correlations between CXCL11 expression and other immune checkpoint markers, such as PD-1, PD-L1, or CTLA-4. Understanding these interactions could provide deeper insights into the immune landscape of colorectal cancer and help determine whether CXCL11 expression influences the effectiveness of immunotherapy strategies. Future research should investigate the potential of CXCL11 as a predictive biomarker for immune checkpoint inhibitor response or as a therapeutic target in combination with immunotherapy.

This study suggest that CXCL11 plays a complex and dynamic role in colorectal cancer progression, with higher expression in early stages potentially promoting immune infiltration and anti-tumor responses, while lower expression in advanced stages may facilitate immune escape and metastasis. However, further research is needed to expand the sample size to improve statistical reliability and validate the findings in larger, multi-center studies. Including normal tissue controls would help establish a clinically meaningful CXCL11 cut-off point for diagnostic and prognostic purposes. Additionally, investigating the mechanistic role of CXCL11 in immune modulation and its interaction with key components of the tumor microenvironment could provide valuable insights into its function. Future studies should also explore CXCL11's relationship with immune checkpoint pathways to assess its potential as a biomarker for immunotherapy response or as a therapeutic target in combination with immune-based treatments. By addressing these aspects, future research could offer a more comprehensive understanding of CXCL11's role in colorectal cancer and enhance its clinical relevance in diagnosis, prognosis, and targeted therapy.

Conclusion

This study demonstrates a significant association between CXCL11 gene expression and metastasis in colorectal cancer patients. Additionally, CXCL11 gene expression varies significantly across different stages of CRC. However, no significant differences were observed between CXCL11 expression and factors such as age, gender, pathological findings, or tumor location. Further research is recommended to explore the potential role of the CXCL11 gene in antitumor therapy.

Data Sharing Statement

All data and tables supporting the findings of this study are provided within the article and can be accessed upon request by contacting the corresponding author.

Ethical Declaration

This study was approved by the Ethics Committee of Hasan Sadikin General Hospital (Approval No. DP.04.03/D. XIV.6.5/360/2024). Informed consent was not obtained directly from the patients, as the specimens were sourced from a tissue bank and data were extracted from medical records. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ensuring patient confidentiality and data protection throughout the research process.

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Disclosure

The authors declare that they have no conflicts of interest related to this paper.

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