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Review Article

Research Progress on the Role of Inflammatory Factors in the Prognosis of Cholangiocarcinoma

Huabing Fan^#, Lixin Liu^#, Songquan Huang^, Lu Chen^, Siheng He^, Zifan Wang^, Lianghua Li^, Yu Chen^, Xiaowen Zhang^* and Sheng Hu^*

The Second Affiliated Hospital of Kunming Medical University, China

***Corresponding author:** Xiaowen Zhang, Sheng Hu, The Second Affiliated Hospital of Kunming Medical University, Kunming, China.

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Abstract

Cholangiocarcinoma (CCA) is the second most common primary hepatobiliary malignancy after hepatocellular carcinoma and remains a highly aggressive cancer with an insidious onset and poor prognosis. Inflammatory Factors (IFs) are critical mediators of immune and inflammatory responses and are increasingly recognized as key contributors to tumor initiation, progression, and therapeutic resistance. Accumulating evidence suggests that elevated circulating levels of inflammatory factors are associated with adverse clinical outcomes in patients with CCA and may serve as independent predictors of unfavorable long-term prognosis. Accordingly, preoperative assessment of inflammatory factors may provide prognostically informative signals and assist in risk stratification. This review summarizes recent advances in the prognostic significance and therapeutic implications of inflammatory factors in cholangiocarcinoma.

Keywords: Cholangiocarcinoma, Inflammatory factors, Cytokines, Prognosis, Tumor microenvironment, IL-6; TNF-α

Abbreviations: CCA: Cholangiocarcinoma; IFs: Inflammatory factors; IL: Interleukin; TNF-α: Tumor necrosis factor-α; JAK/STAT3: Janus kinase/signal transducer and activator of transcription 3; NF-κB: Nuclear factor kappa B; CRP: C-reactive protein; GPS: Glasgow Prognostic Score; SII: Systemic Immune-Inflammation Index; PD-1/PD-L1: Programmed cell death 1 / programmed death-ligand 1

Introduction

Cholangiocarcinoma (CCA) is a malignant tumor arising from biliary epithelial cells, accounting for approximately 10%-20% of hepatobiliary malignancies and about 3% of digestive system cancers. Although CCA is relatively uncommon, its incidence and mortality have increased worldwide over recent decades [1]. For patients with resectable disease, radical resection with negative margins (R0 resection) remains the only potentially curative option. However, due to its insidious clinical presentation, early detection is challenging and many patients are diagnosed at an advanced stage. As a result, only a minority are eligible for surgery, and the postoperative 5-year survival rate is approximately 20%-40%.

Inflammation is a physiological defense response against tissue injury and infection [2-6]. During inflammation, infiltrating immune cells (e.g., neutrophils and macrophages) can release Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), which may damage DNA, increase mutational burden, and contribute to carcinogenesis [2,5]. Circulating inflammatory factors and inflammation-related indices have shown prognostic value across multiple malignancies, including cervical cancer, gastric cancer, lung cancer, and HCC. Current evidence also supports a relationship between serum IFs and CCA outcomes, where higher IF levels are generally associated with worse long-term prognosis [3,4,6]. Moreover, combining IFs with other biomarkers is increasingly recognized as a practical strategy to improve risk stratification. This review summarizes (i) the expression patterns and prognostic relevance of IFs in CCA, (ii) their potential roles in CCA treatment, and (iii) their combined application with other prognostic indicators.

Discussion

Biological Roles of Inflammatory Factors: Benefits and Limitations

Inflammatory factors are central mediators of the immune response and play essential roles in host defense and tissue repair under physiological conditions [7,8]. When tissues are injured or invaded by pathogens, immune cells release inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-alpha), interleukin-1 (IL-1), and interferons, among others [9]. These mediators help

eliminate threats, limit the spread of damage, and promote healing by recruiting immune cells to sites of injury, increasing vascular permeability, activating antimicrobial programs, and initiating tissue repair.

However, when inflammatory signaling becomes dysregulated, inflammatory factors can shift from protective mediators to drivers of pathology. Excessive production, prolonged persistence (as in chronic inflammation), or misdirected immune activation against self-tissues can lead to substantial tissue injury [2]. Persistent inflammation has been implicated in diverse diseases: it can damage vascular endothelium and accelerate atherosclerosis, contributing to cardiovascular and cerebrovascular events; disrupt insulin signaling pathways (e.g., via inhibitory serine/threonine phosphorylation of IRS-1), promoting insulin resistance and type 2 diabetes; and sustain synovial inflammation in rheumatoid arthritis. Importantly, chronic inflammatory signaling can also continuously stimulate cell proliferation and genetic instability, thereby increasing cancer risk [3,10]. Thus, inflammatory factors represent a classic 'double-edged sword' that requires tight regulation to maintain health.

Expression of Inflammatory Factors in Cca and Prognostic Implications

Inflammatory factors - particularly pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-1beta - can help shape a tumor-promoting milieu that supports sustained proliferation and suppresses programmed cell death (apoptosis) [11]. Many inflammatory mediators also have potent pro-angiogenic effects, facilitating neovascularization that supplies oxygen and nutrients required for tumor expansion. Conversely, acute inflammation and certain cytokines (e.g., type I interferons and IL-12) can enhance anti-tumor immunity, underscoring the context-dependent roles of inflammatory signaling [3]. In CCA, tumors can exploit inflammatory processes to support growth and metastasis, while immune cells within the inflammatory microenvironment may indirectly promote progression and dissemination [12,3,13].

Among these mediators, interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-alpha) are frequently highlighted as core drivers of CCA progression. In chronic biliary diseases such as hepatolithiasis and primary sclerosing cholangitis, these cytokines contribute to a persistent inflammatory microenvironment and promote carcinogenesis through key signaling pathways [13]. IL-6 activates the JAK/STAT3 axis, enhancing CCA cell proliferation and survival and conferring resistance to apoptosis; it can also promote the accumulation of myeloid-derived suppressor cells, thereby fostering an immunosuppressive microenvironment that facilitates tumor immune evasion [12,14-17]. TNF-alpha acts primarily through the NF-kappaB pathway, promoting invasion, metastasis, and angiogenesis, and synergizes with other mediators to maintain a pro-oncogenic inflammatory state [13]. Importantly, these pathways can reinforce each other: TNF-alpha can induce IL-6 production, which in turn amplifies inflammatory signaling, creating a self-sustaining loop that remodels the tumor microenvironment and supports disease progression [18]. Multiple studies have reported that elevated preoperative serum IFs (e.g., TNF-alpha and IL-6) are associated with poor prognosis in CCA [19,14,18]. High IF levels have also been linked to TNM stage and lymph node metastasis, and may serve as independent risk factors for unfavorable long-term outcomes [14].

Therapeutic implications of targeting inflammatory factors

The clinical role of inflammatory factors in CCA is evolving from prognostic biomarkers to therapeutic targets and key components of combination strategies. A central concept is to disrupt chronic inflammatory circuits that promote tumor growth and immune suppression [5,20]. Current approaches can be considered at three levels. First, direct inhibition of key cytokines or their receptors, such as targeting the IL-6 receptor (e.g., tocilizumab) or using TNF-alpha inhibitors. In principle, combining IL-6 blockade with standard chemotherapy (e.g., gemcitabine plus cisplatin) may attenuate the core proliferative and immunosuppressive signaling mediated by JAK/STAT3 [20]. Second, inhibition of downstream convergent pathways, including STAT3, NF-kappaB, and COX-2/PGE2, using small-molecule agents (e.g., napabucasin) that can broadly counteract pro-tumor inflammation [21-23]. Third, combining anti-inflammatory interventions (e.g., celecoxib) with immune checkpoint blockade (e.g., PD-1/PD-L1 antibodies), which is a rapidly advancing direction. Because high levels of IL-6, TNF-alpha, and other cytokines can establish an immunosuppressive microenvironment that contributes to resistance to immunotherapy, anti-inflammatory strategies may 'reprogram' the microenvironment and enhance immune responses [11,24]. In addition, circulating inflammatory markers such as C-Reactive Protein (CRP) and IL-6 can potentially support dynamic monitoring of treatment response and prognosis [25]. Overall, therapeutic strategies targeting inflammatory signaling provide a promising avenue to address the aggressive biology and limited treatment options of CCA, particularly through rational combination regimens aimed at breaking the cycle of inflammation, immunosuppression, and tumor progression [20].

Integrating inflammatory factors with other biomarkers

Inflammatory factors are not specific to CCA and can also be elevated in other inflammatory conditions or organ diseases, limiting their performance as standalone biomarkers [2,9]. Therefore, prognostic assessment increasingly integrates IFs with conventional and emerging indicators to build more accurate and multidimensional models [25]. Rather than a simple additive approach, these combinations integrate biological information from complementary domains to better capture tumor aggressiveness and host immune status, thereby overcoming the limitations of single markers and improving predictive accuracy (a practical '1 + 1 > 2' effect) [25-28].

In practice, combined applications can be summarized in three areas. First, integration with standard clinicopathological parameters. For example, elevated IL-6 or CRP together with increased CA19-9, lymph node metastasis, and advanced stage can improve postoperative risk stratification [25]. IL-6 reflects

systemic inflammation and immunosuppression, complementing anatomical staging that may not fully capture tumor biology. Second, integration with molecular biomarkers and tumor subtyping. Linking inflammatory markers (e.g., neutrophil-to-lymphocyte ratio, NLR) with actionable alterations (e.g., IDH1/2 mutations or FGFR2 fusions) and immune context (e.g., PD-L1 expression and CD8+ T-cell infiltration) may help define clinically meaningful subgroups and inform targeted or immunotherapy strategies. Third, the use of composite inflammation-based scoring systems. Examples include the Glasgow Prognostic Score (GPS), which combines CRP and albumin [29,30], and the Systemic Immune-Inflammation Index (SII) derived from multiple blood parameters (e.g., NLR and platelet-to-lymphocyte ratio, PLR). These composite indices have repeatedly been validated as stronger independent prognostic factors than single inflammatory cytokines, as they simultaneously quantify systemic inflammation, nutritional status, and immune competence [31].

Conclusion

Inflammatory factors centered on IL-6 and TNF-alpha play fundamental roles in the initiation, progression, and immune evasion of cholangiocarcinoma [13]. They serve not only as prognostic biomarkers but also as promising therapeutic targets. Current research has moved from mechanistic exploration to early clinical translation, including targeting cytokines themselves, inhibiting key downstream pathways, and combining anti-inflammatory approaches with immunotherapy [5,20].

Future directions in this field are likely to focus on: (i) personalization and precision, including defining inflammatory signatures across molecular subtypes (e.g., IDH-mutant or FGFR-fused CCA) to guide the selection of effective anti-inflammatory combinations; (ii) overcoming therapeutic resistance by characterizing how the inflammatory microenvironment evolves under targeted therapy or immunotherapy and identifying rational co-treatment strategies; and (iii) system-level integration of anti-inflammatory interventions into multimodal CCA management. Prospective clinical trials are needed to clarify the optimal timing, patient selection, and clinical benefit of these strategies across perioperative and advanced disease settings, with the overarching goal of disrupting the cycle of inflammation, immunosuppression, and tumor progression to improve outcomes in this challenging malignancy.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review.

References

of intrahepatic cholangiocarcinoma. BMC Cancer 23(1):188.

1. Samantha Sarcognato, Diana Sacchi, Matteo Fassan, Luca Fabris, Massimiliano Cadamuro, et al. (2021) Cholangiocarcinoma. Pathologica 113(3): 158-169.
2. Jeanette A Maier, Sara Castiglioni, Alessandra Petrelli, Rosanna Cannatelli, Francesca Ferretti, et al. (2024) Immune-mediated inflammatory diseases and cancer - a dangerous liaison. Front Immunol 15: 1436581.
3. Pradhan R, Kundu A, Kundu CN (2024) The cytokines in tumor microenvironment: From cancer initiation-elongation-progression to metastatic outgrowth. Crit Rev Oncol Hematol 196: 104311.
4. Emmanouil Bouras, Ville Karhunen, Dipender Gill, Jian Huang, Philip C Haycock, et al. (2022) Circulating inflammatory cytokines and risk of five cancers: A Mendelian randomization analysis. BMC Med 20(1): 3.
5. Yifei Xie, Fangfang Liu, Yunfei Wu, Yuer Zhu, Yanan Jiang, et al. (2025) Inflammation in cancer: Therapeutic opportunities from new insights. Mol Cancer 24(1): 51.
6. James Yarmolinsky, Jamie W Robinson, Daniela Mariosa, Ville Karhunen, Jian Huang, et al. (2024) Association between circulating inflammatory markers and adult cancer risk: A Mendelian randomization analysis. eBioMedicine 100: 104991.
7. Rindlisbacher L, Navarro MN, Becher B (2026) Inflame and restrain - the paradoxical roles of IL-12 and IL-23 in immunity. Nat Rev Immunol.
8. Goleij P, Amini A, Tabari MAK (2025) Unraveling the role of the IL-20 cytokine family in neurodegenerative diseases: Mechanisms and therapeutic insights. Int Immunopharmacol 152: 114399.
9. Zheng J, Mao H, Chong WP (2025) Editorial: Unraveling the molecular mechanisms of cytokine signaling in regulating inflammatory diseases. Front Immunol 16: 1563469.
10. Xian Pei Xiao, Ming Yu Wu, Yan Li, Xiao Hu, Bi Yuan Qin, et al. (2026) Global landscape of autoimmune diseases across different lifespan: A three-decade perspective. Medicine 105(2): e47140.
11. Maemura K, Natsugoe S, Takao S (2014) Molecular mechanism of cholangiocarcinoma carcinogenesis. J Hepatobiliary Pancreat Sci 21(10): 754-760.
12. Troels D Christensen, Kasper Madsen, Emil Maag, Ole Larsen, Lars Henrik Jensen, et al. (2023) Protein signatures and individual circulating proteins, including IL-6 and IL-15, associated with prognosis in patients with biliary tract cancer. Cancers 15(4): 1062.

13. Glauben Landskron, Marjorie De la Fuente, Peti Thuwajit, Chanitra Thuwajit, Marcela A Hermoso, et al. (2014) Chronic inflammation and cytokines in the tumor microenvironment. J Immunol Res: 1-19.

14. Dongqing Gu, Xin Zhao, Jing Song, Jianmei Xiao, Leida Zhang, et al. (2024) Expression and clinical significance of interleukin-6 pathway in cholangiocarcinoma. Front Immunol 15: 1374967.

15. Boryana Georgieva, Danijela Karanović, Ivona Veličković, Danail Minchev (2025) Multifaceted roles of IL-26 in physiological and pathological conditions. Int J Mol Sci 27(1): 325.

16. Meng Zhou, Ruisi Na, Shihui Lai, Ying Guo, Jiaqi Shi, et al. (2023) The present roles and future perspectives of interleukin-6 in biliary tract cancer. Cytokine 169: 156271.

17. Jan Hrudka, Radoslav Matěj (2025) Cholangiokarcinom - morfologie, imunohistochemie, genetika. Cesk Patol 61(3): 148-158.

18. Kangsadan Chueajedton, Chaiwat Chueaiphuk, Jeranan Inpad, Sarawut Kumphune, Worasak Kaewkong, et al. (2026) Secretory leukocyte protease inhibitor (SLPI) promotes cholangiocarcinoma progression via inflammation-associated and vasculogenic mechanisms. PLoS One 21(1): e0340763.

19. Toshio Hirano (2021) IL-6 in inflammation, autoimmunity and cancer. Int Immunol 33(3): 127-148.

20. Stephen L Chan, Angela Lamarca, Chiun Hsu, Victor Moreno, Landon L Chan, et al. (2026) New targets and new drugs for hepatobiliary cancers. J Hepatol 84(1): 213-228.

21. Qing Guo, Yizi Jin, Xinyu Chen, Xiaomin Ye, Xin Shen, et al. (2024) NF-κB in biology and targeted therapy: New insights and translational implications. Signal Transduct Target Ther 9(1): 53.

22. Joseph A DiDonato, Frank Mercurio, Michael Karin (2012) NF-κB and the link between inflammation and cancer. Immunol Rev 246(1): 379-400.

23. Feng Ping Kang, Zhi Wen Chen, Cheng Yu Liao, Yong Ding Wu, Ge Li, et al. (2024) Escherichia coli-induced stress granules activate NF-κB to promote intrahepatic cholangiocarcinoma progression. Adv Sci 11(16): 2306174.

24. Manoj Kumar Yadav, Samara P Singh, Charles E Egwuagu (2025) IL-6/IL-12 superfamily of cytokines and regulatory lymphocytes play critical roles in the etiology and suppression of CNS autoimmune diseases. Front Immunol 16: 1514080.

25. Bo Hao Zheng, Liu Xiao Yang, Qi Man Sun, Hong Kai Fan, Men Duan, et al. (2017) A new preoperative prognostic system combining CRP and CA19-9 for patients with intrahepatic cholangiocarcinoma. Clin Transl Gastroenterol 8(10): e118.

26. Yinghao Lv, Hu Liu, Penghui He, Sinan Xie, Xiuchun Yin, et al. (2023) A novel model for predicting the prognosis of postoperative intrahepatic cholangiocarcinoma patients. Sci Rep 13(1): 19267.

27. Jian Ping Xiong, Jun Yu Long, Wei Yu Xu, Jin Bian, Han Chun Huang, et al. (2019) Albumin-to-alkaline phosphatase ratio: A novel prognostic index of overall survival in cholangiocarcinoma patients after surgery. World J Gastrointest Oncol 11(1): 39-47.

28. Feng Zhang, Shenxin Lu, Mengxin Tian, Keshu Hu, Rongxin Chen, et al. (2020) Albumin-to-alkaline phosphatase ratio is an independent prognostic indicator in combined hepatocellular and cholangiocarcinoma. J Cancer 11(17): 5177-5186.

29. Masashi Tsunematsu, Koichiro Haruki, Tomohiko Taniai, Yoshiaki Tanji, Yoshihiro Shirai, et al. (2023) The impact of the CALLY index on prognosis of distal cholangiocarcinoma following pancreaticoduodenectomy. Ann Gastroenterol Surg 7(3): 503-511.

30. Tokuji Ito, Hiroji Shinkawa, Shigekazu Takemura, Shogo Tanaka, Takayoshi Nishioka, et al. (2020) Impact of the preoperative C-reactive protein to albumin ratio on long-term outcomes of hepatic resection for intrahepatic cholangiocarcinoma. Asian Pac J Cancer Prev 21(8): 2373-2379.

31. Jun Fu, Qinjunjie Chen, Zisen Lai, Kongying Lin, Guoxu Fang, et al. (2023) A novel preoperative inflammation score system for postoperative prognosis prediction BMC Cancer 23(1): 188.