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CHOLANGIOCARCINOMA: A COMPREHENSIVE OVERVIEW OF EPIDEMIOLOGY, PATHOGENESIS, DIAGNOSIS, AND TREATMENT

Michał Wabiszczewicz[1] ✉, ***Albert Lompart[2]***, ***Albert Kosarewicz[3]***, ***Łukasz Woźniak[4]***, ***Patrycja Krysiak[5]***

[1]Medunit Primary Care Clinic, Gdańsk, Poland
[2]Saint Wojciech Hospital, Gdańsk, Poland
[3]University Clinical Centre of Gdańsk Medical University, Gdańsk, Poland
[4]West Pomeranian Center for the Treatment of Severe Burns and Plastic Surgery, Gryfice, Poland
[5]Medical University of Łódź, Łódź, Poland

✉ ***michalwabi@gmail.com***

ABSTRACT

BACKGROUND:

Cholangiocarcinoma (CCA) is an uncommon yet highly aggressive malignancy of the biliary tract, typically diagnosed at advanced stages and associated with poor outcomes. Its incidence continues to rise worldwide, particularly for intrahepatic CCA. Progress in molecular profiling and precision oncology has enabled the introduction of targeted therapies, although inequalities in diagnostic and therapeutic access persist.

AIM OF THE STUDY:

The objective of this review is to integrate current evidence on the epidemiology, molecular pathogenesis, diagnostic strategies, and treatment of CCA, with particular attention to actionable molecular alterations, targeted therapies, and the role of personalized medicine.

MATERIALS AND METHODS:

A narrative review of the English-language literature (2021–2025) was performed using PubMed, Scopus, PMC, and Google Scholar. Articles were selected if they addressed molecular biomarkers (e.g., FGFR2, IDH1), novel diagnostic tools, or systemic therapies. Priority was given to phase II/III clinical trials, real-world data, and emerging technologies such as liquid biopsy and AI-based histopathology.

RESULTS:

Targetable alterations including FGFR2 fusions and IDH1 mutations have reshaped therapeutic strategies in intrahepatic CCA. Agents such as pemigatinib and ivosidenib have shown meaningful clinical activity, with real-world data confirming meaningful clinical benefit in patients with FGFR2 fusions. Advances in next-generation sequencing and liquid biopsy have enhanced diagnostic precision and disease monitoring. Nevertheless, major barriers remain, including delayed molecular testing, limited availability of clinical trials, and development of

resistance mechanisms.

CONCLUSIONS:

Although treatment innovations have improved outcomes for selected patients, CCA continues to be a highly lethal malignancy with significant unmet needs. Broader implementation of molecular diagnostics, equitable access to targeted therapies, and earlier intervention are crucial. Future work must also address resistance pathways and promote inclusive research to fully realize the potential of precision oncology in cholangiocarcinoma.

Keywords: Cholangiocarcinoma, Bile Duct Neoplasms, FGFR2 fusions, IDH1

mutations, Molecular Targeted Therapy, Liquid Biopsy, Immunotherapy

1. INTRODUCTION

Cholangiocarcinoma is a malignant tumor that originates from the bile epithelium, which represents the second most common primary liver cancer after hepatocellular carcinoma [1] Classified as intrahepatic or extrahepatic anatomically, this disease shows diverse molecular and clinical behavior. Although it is still considered rare in most Western populations, with occurrences below two per 100,000, its global incidence has increased regularly over the past three decades, especially in East Asia and South America. In Europe, the incidence of cholangiocarcinoma ranges from approximately 0.5 to 3.4 cases per 100 000 population, with intrahepatic cholangiocarcinoma showing the most pronounced increase [1]. Mortality analyses have also demonstrated a steeper rise in Eastern European countries compared to Western Europe [2]. In Poland, according to the National Cancer Registry, 171 558 new cancer cases and 93 652 cancer-related deaths were recorded in 2021, underscoring the oncological burden in the region [3]. The etiology of cholangiocarcinoma is multifactorial. Established risk factors include liver fluke infections, hepatobiliary diseases such as primary sclerosing cholangitis and hepatolithiasis, viral hepatitis, cirrhosis, diabetes, and obesity [4]. Chronic inflammation is a common mechanism across these associations. Geographical hotspots such as Thailand have very high rates of Opisthorchis viverrini exposure among the rural population [4] Morbid outcomes are specific because most patients present with advanced-phase disease and have limited treatment options, resulting in low five-year survival rates lower than 20 percent [4]. In recent years, molecular profiles, FGFR2 fusions, IDH1 mutation targeted remedies, and mild progress have been seen through the integration of immunotherapy [5]. However, challenges such as late diagnosis, limited access to testing, and regional treatment inequality persist.

1.2. PURPOSE OF RESEARCH

The purpose of this review is to synthesize recent advances in cholangiocarcinoma by presenting current insights into its epidemiology, pathogenesis, diagnostic approaches, and treatment options, with a focus on molecular mechanisms and the emergence of targeted and immunotherapeutic strategies.

2. RESEARCH MATERIALS AND METHODS SECTION

This review applied a structured methodology to evaluate recent scientific work published between 2021 and 2025 on cholangiocarcinoma, focusing on epidemiology, pathogenesis, diagnostics, and treatment. We conducted targeted searches in PubMed, Scopus, Google Scholar, and PMC using keywords including "Cholangiocarcinoma", "FGFR2‟, "IDH1”, " Diagnosis”, "Treatment”, and "Targeted Therapy". Boolean operators combined terms to ensure a robust catch of relevant literature, such as FGFR2 issues in intrahepatic cholangiocarcinoma (Chen and FGFR2) and CA19-9 in diagnosis (Ca19-9 and Cholangiocarcinoma diagnosis). Additional filters selected peer-reviewed English studies with full text, including clinical studies, systematic reviews, and original research.

The initial search retrieved over 180 articles. Titles and abstracts were screened to exclude editorial comments and pediatric studies. For deeper analysis, 110 articles were reviewed in full text. Studies were included if they directly addressed molecular targeted therapy with genomic profiling, biomarker-based diagnosis, or regional epidemiological trends. Finally, 30 sources were chosen for detailed synthesis.

Data extraction held studies design, patient demographics, sample size, molecular findings, treatment reactions, and results. Treatment-focused studies included decisive studies such as Fight-202 Pemigatinib phase II studies, which used genomic profiles to identify FGFR2 fusions patients [6]. The real-world results from pemigatinib from the PEMI-BIL and PEMI-REAL cohorts were also analyzed [7]. The IDH1 inhibitory efficacy data were captured by clinical studies such as ClarIDHy, while the FDA approval deadline for pemigatinib, futibatinib, and infigratinib was confirmed through US FDA announcements. Comparative effectiveness of FGFR inhibitors, including ORR and PFS data, was included by a multicenter studies and PMC Meta-Analysis [8]. The CAD system and AI tools for clinical histopathology were also evaluated through

technical reviews.

Epidemiological trends were obtained from global cancer registries and field-specific studies, which compared changes in events in Asia, Europe, and North America, and addressed risk factors such as Opisthorchis viverrini in regions such as Thailand [8]. Data from clinical biomarkers included CA19-9, CEA, and novel liquid biopsy approaches, analyzed through clinical research. Data synthesis followed the story's review model, merging quantitative conclusions with qualitative analysis to highlight advances, stability, and knowledge gaps. In molecular diagnosis and targeted medical access, geographical differences and limitations were also examined, referring to equity and resource-based views. The relevant clinical guidelines and regulatory approval were quoted to ensure currency. This carefully curated review captures the developing landscape of cholangiocarcinoma research. The studies gather a strong evidence base for using genomic biomarkers and targeted therapy while identifying sustained challenges such as late presentation, diagnostic holes, limited molecular testing, drug resistance, and treatment differences. These findings inform the synthesis of epidemiological, biological, diagnostic, and therapeutic best practices and control future research directions and clinical strategies.

3. FINDINGS

3.1. EPIDEMIOLOGY OF CHOLANGIOCARCINOMA

The second most common primary liver cancer, Cholangiocarcinoma, has been growing globally over recent decades. The incidence of intrahepatic Cholangiocarcinoma (ICCA) has increased in Western Europe and North America, while extrahepatic Cholangiocarcinoma (ECCA) is stable or reduced [4]. In the United States, rates climbed from approximately 11.98 to over 12 per 100,000 person-years between 2000 and 2015. Before stability after 2013, mortality rose to an annual percentage of about 6 percent [9]. Despite its rarity, about 1 to 2 cases per 100,000 annually occur in the West, where mortality is higher, of which 5-year survival is less than 20 percent, mainly because the diagnosis often occurs at an advanced stage.

Geographically, South East Asia, especially Thailand and Laos, displays some of the highest rates in the world, up to 100 per 100 000, of spatial liver fluid infections (Opisthorchis viverrini and Clonorchis sinensis) and associated biliary inflammation (Global CCA Alliance). Thailand saw a decline in cancer rates in the last decade, 6.1 per 100,000 in men with estimated incidents for 2026 and 3.4 in women 3.4 [10]. Age, gender, and socioeconomic factors also affect the event pattern. Most cases are present after the age of 60, with a slightly higher prevalence in males. Disparities have been documented among underrepresented populations in the United States; for example, Hispanic and Indigenous groups have a significantly greater cholangiocarcinoma burden that is often associated with environmental and socioeconomic inequities [11]. Other major risk factors include chronic biliary inflammation, primary sclerosing cholangitis, congenital cystic biliary anomalies, hepatolithiasis, chronic hepatitis, or cirrhosis. Metabolic conditions comprise diabetes and obesity, plus nonalcoholic fatty liver disease, which has recently been considered a strong contributor to the risk of iCCA.

3.2. PATHOGENESIS AND MOLECULAR MECHANISMS

Chronic inflammation and cholestasis play a central role in the molecular pathogenesis of cholangiocarcinoma. Persistent inflammation of the bile duct leads to a high level of interleukin 6, tumor necrosis factor-alpha, and COX 2, which activate signaling pathways such as JAK STAT, MAPK, and PI3K AKT, which in turn promote the cellular spread and prevent apoptosis. SOCS3 silencing through epigenetics means uncontrolled Stat3 activation further stimulates cancer cell survival [12]. Additionally, biliary acid accumulation from cholestasis activates NF κB and Wnt/β catenin signaling, contributing to genomic instability and the anti-apoptotic system through COX 2 and MCL 1 height. KRAS mutation and G9A-armed epic reprogramming have been linked to metabolic changes and interleukin-6 overproduction, which promotes [12]

FGFR2 gene fusions occur in about 10-15 percent of intrahepatic cholangiocarcinomas. These fusions activate downstream signaling pathways such as RAS, MAPK, and PI3K-AKT, and patients whose tumors harbor FGFR2 fusions generally have better outcomes with standard therapies and are sensitive to FGFR-targeted therapies [13]. Mutations of DH1 identified only in some tumors cause the build-up of the oncometabolite 2-hydroxyglutarate, resulting in epigenetic deregulation and blockade of cellular differentiation. MicroRNAs such as miR-26a also activate Wnt/β catenin signaling, further promoting tumor growth and survival. Emerging immune subtypes identified through transcriptomic analysis highlight macrophage metabolism and immune filtration variations, suggesting new paths for immunotherapy development and prognostic storage [14]. These collective molecular drivers emphasize the complexity of cholangiocarcinogenesis and inform about the design of precision diagnostic tools and targeted treatment strategies.

3.3. DIAGNOSTIC APPROACHES

Diagnosing cholangiocarcinoma often requires a combination of imaging, tissue sampling, and emerging

molecular devices due to its complex presentation. According to [15], imaging modalities such as CT, MRI, and MRCP are usually the first step, which helps to detect strictures or masses in the Galleries. However, although these methods are useful for identifying suspicious lesions, they cannot provide a definitive diagnosis. For tissue sampling, endoscopic retrograde cholangiopancreatography is usually used to obtain brushing or biopsy, showing clinical sensitivity from 56 Percent when brush cytology is used alone, with 70 percent when brush cytology is combined with forceps biopsy [15]. Percutaneous transhepatic cholangiography can be an option, especially when endoscopic access is limited, allowing biopsy and drainage but increasing the risk of complications.

Endoscopic ultrasound with fine-needle aspiration has emerged as a sensitive method, especially for the distal bile and peripheral pulp. The sensitivity is between 70 and 80 percent, and it also enables lymph node staging without crossing the peritoneum, such as the risks of the tumor's Beijing [16]. Intraductal ultrasound enhances further detection, provides sensitivity and specificity above 90 percent for the proximal bile duct's strictness, and improves ERCP's clinical accuracy.

Advanced techniques, among them cholangioscopy, permit direct visualization and targeted biopsy with an accuracy level of about 85 to 95 percent. Emerging molecular diagnostics, especially a liquid biopsy by sequencing cell-free DNA from bile, have promising sensitivity, up to 96 percent as opposed to only about 42 percent for conventional cytology [17]. Standard imaging combined with tissue sampling and molecular techniques should significantly increase the acumen of diagnosis and allow for earlier detection in many cases. These diagnostic approaches are summarized in Table 1, which compares their sensitivity, specificity, and clinical application.

Table 1. Diagnostic methods for cholangiocarcinoma: comparison of performance, advantages, and limitations

Method	Use Case	Sensitivity	Specificity	Advantages	Limitations
CT / MRI / MRCP	First-line imaging for masses or strictures	~75%	~85%	Non-invasive, good visualization	Cannot confirm malignancy
ERCP + Brush Cytology	Tissue sampling via endoscopy	56%	High	Accessible, drainage possible	Low sensitivity alone
ERCP + Brush + Biopsy	Combined cytology and histology	70%	High	Improved accuracy	Invasive, skill-dependent
Percutaneous Cholangiography	Alternative access when ERCP fails	Variable	High	Useful when ERCP inaccessible	Higher complication risk
EUS-FNA	Distal bile duct and lymph nodes	70–80%	High	Staging + sampling in one	Limited for hilar lesions
Intraductal Ultrasound	Proximal duct strictures	>90%	>90%	Enhances ERCP accuracy	Limited availability
Cholangioscopy	Direct visualization and biopsy	85–95%	High	Targeted biopsy	Expensive, requires expertise
Liquid Biopsy (cfDNA in bile)	Molecular mutation detection	Up to 96%	High	Non-invasive, promising	Still under validation

cfDNA – cell-free DNA; ERCP – Endoscopic Retrograde Cholangiopancreatography; EUS-FNA – Endoscopic Ultrasound–Fine Needle Aspiration; MRCP – Magnetic Resonance Cholangiopancreatography.

3.4. STAGING AND PROGNOSTIC FACTORS

Cholangiocarcinoma is staged through the AJCC/UICC TNM system or models that are more oriented toward clinical aspects, including tumor characteristics and patient performance status. In the eighth edition of the AJCC classification, tumor size, multiplicity, vascular invasion, lymph node involvement, and metastasis status are included because of their significant impact on outcome prediction [18]. Validation studies indicate that this version discriminates better than earlier versions, particularly in terms of differentiation among stage III subtypes. Prognostic factors are tumor number, nodal metastasis, and vascular invasion, which are associated with poorer survival independently [19]. Clinical scoring systems that add factors such as albumin levels, CA 19-9, ECOG status, and tumor burden further refine the risk stratification. In this model, patients were stratified into four prognostic groups, with 1-year survival noted to be between 87 percent in the early stage and 16 percent in advanced disease [20]. This layered staging helps guide treatment planning from surgery to systemic therapy.

3.5. TREATMENT MODALITIES

Cholangiocarcinoma therapy depends on the disease stage and molecular characteristics. Surgical resection is still the primary curative option. When lesions are located, complete removal offers the best chance of long-term survival, although fewer than thirty percent of cases are resectable. For unresectable or metastatic disease, standard first-line treatment, gemcitabine, is combined with cisplatin. The ABC-02 study set this regimen as a gold standard and demonstrated modest survival improvement [21]. Recently, the addition of the

immunotherapy agent durvalumab to gemcitabine and cisplatin in the TOPAZ 1 regimen significantly improved the total survival, which led to adoption as the new standard for advanced cancer in the bile tract [21]. Advances in precision medicine have introduced targeted therapies for specific genetic mutations. Pemigatinib, an FGFR1/3 inhibitor, got accelerated FDA approval in 2020 for patients with FGFR2 fusion–positive cholangiocarcinoma. The FIGHT 202 phase II trial showed an objective response rate of 35 percent and a median progression-free survival of seven months, with acceptable tolerance [21]. Futibatinib, a next-generation irreversible FGFR1 4 inhibitor, received approval in 2022 after achieving a 42 percent response rate and median progression-free survival of 8.9 months in the FOENIX CCA2 trial [22]. Other options include IDH1 inhibitors such as ivosidenib, which was approved in 2021 for IDH1 mutant Cholangiocarcinoma, showing improved progression-free survival compared to the placebo patients in the ClarIDHy trial. Locoregional approaches such as photodynamic therapy, radioembolization, and transarterial chemoembolization also provide a palliative advantage, especially for untrained intrahepatic tumors, and help to relieve symptoms of bile obstruction. These modalities extend disease control and quality of life for patients not eligible for surgery or systemic treatment.

As shown in Table 2, several targeted therapies have been approved for FGFR2- and IDH1-altered cholangiocarcinoma, based on phase II and III trials.

Table 2. Overview of FDA-approved targeted therapies in FGFR2- and IDH1-altered cholangiocarcinoma.

Therapy	Target	Trial (Phase)	ORR (%)	PFS (months)	Approval Status
Pemigatinib	FGFR2	FIGHT-202 (Phase II)	35%	7.0	FDA approved
Futibatinib	FGFR2	FOENIX-CCA2 (Phase II)	42%	8.9	FDA approved
Ivosidenib	IDH1	ClarIDHy (Phase III)	5%	2.7 vs 1.4	FDA approved

ORR – Objective Response Rate; PFS – Progression-Free Survival; FDA – U.S. Food and Drug Administration

3.6. ADVANCES IN PERSONALIZED AND PRECISION MEDICINE

Molecular profiling radically changes the treatment approaches with personalized, targeted therapies in cholangiocarcinoma. FGFR2 fusions observed in approximately 10 to 15% of cases are newly targetable with agents like pemigatinib. It is reported in the FIGHT-202 trial that an objective response rate came along with a median progression-free survival of close to 7 months for patients having those genetic alterations, which reinforces the indication for genomic sequencing to guide therapy [6]. Real-world data from Chinese cohorts replicates these results, reporting a 50% response rate and a 6.3-month median progression-free survival, indicating unambiguous effectiveness [23]. Liquid biopsy is emerging as a noninvasive method to identify medical mutations using circulating tumor DNA and monitor treatment resistance during therapy. Recent studies have reported detection rates above eighty percent in advanced bile duct cancer. They have a high consensus with tissue-based genomic profiles, making it a promising tool to guide targeted medical decisions [24]. The next-generation sequencing panel and AI-driven diagnosis have been rapidly integrated into clinical practice to support tracking mutation identification and accurate test matching. These emerging approaches increase individual patient care and offer new paths to manage tumor asymmetry and treatment resistance.

3.7. CHALLENGES AND LIMITATIONS

Cholangiocarcinoma is often diagnosed in advanced stages, resulting in poor survival rates of less than ten percent at five years in many cases due to non-specific symptoms and delayed detection. Access to molecular diagnostics and targeted therapies is still limited for many patients. In Scotland, for example, patients with approved targeted medicines cannot receive them without financing for genomic profiling, which highlights systemic barriers to fair care. Tumor heterogeneity and acquired resistance further complicate treatment. Even tumors driven by well-known mutations, such as FGFR2 or IDH1 changes, often develop resistance to targeted medicines over time, reducing the effectiveness of therapy. Additionally, lack of participation in clinical studies increases these problems, especially in the US, where there are frequent racial and socio-economic inequalities in nominations and trials in minority and disadvantaged populations [11]. There are more resource restrictions

in low and medium-income areas that limit advanced images, pathology services, and accessories, often forcing dependence on subcutaneous treatment alone [25]. Tackling these challenges requires improved efforts for early discovery, extended funding for molecular testing, improved trials, and strengthening of the health infrastructure in a resource-limited environment.

3.8. FUTURE RESEARCH DIRECTIONS

The progress of cholangiocarcinoma research focuses on precision oncology, early detection, and increased clinical trial diversity. One of the main areas is a molecular matching study, such as the SAFIR ABC10 trial, which combines patients with targeted therapy and shows promising results, including tumor contraction and extended remission in the next stage of the disease. Parallel efforts are pushing immunotherapy, with bibliometric analysis showing an increasing investigation into connecting immune checkpoint inhibitors with traditional treatments to address the aggressive tumor microelements. Integrating next-generation sequencing and liquid biopsy in clinical practice is another promising frontier. Studies such as MOSCATO 01 have shown an improved existence when rotating Tumor DNA guides therapy selection, and initial clinical data suggest ctDNA detection rates over eighty percent in biliary cancers [26]. Finally, emerging technologies such as cold plasma treatment show the initial effectiveness in motivating the death of the tumor cell in the precursor models of cholangiocarcinoma [27]. Future research should recognize these techniques in large trials and ensure entry into low-resource settings while emphasizing the same incorporation in preliminary investigation, personal treatment, and clinical research.

3.9. BASIC RESULTS

This synthesis exposes the developed landscape in cholangiocarcinoma research, focusing on target therapies, real-world consequences, clinical strategies, and frequent challenges. Pemigatinib, an FGFR inhibitor approved in 2020, has emerged as a foundation for managing FGFR2 fusion–positive cholangiocarcinoma. In Phase II Study-202 study, pemigatinib produced a remarkable partial response rate of 35.5 % of 107 patients, including 2.8 % full responses. The medium duration of the response was 9.1 months, with 63 percent of the responses beyond six months and 18 percent twelve months [28]. These results were comparable when evaluated in real-world settings. A joint French-Italian Cohort of 72 patients recorded 45.8 percent in 84.7 percent and an objective response to the disease control, with an average of 8.7 months of progression-free existence and a one-year survival of 60.6 percent [7]. Similarly, US data from the real world involved 120 patients with a total response rate of 59.2 percent and the real-world progression-free survival (RWPF) median of 7.4 months [29]. This data confirms that Pemigatinib supplies consistent and durable clinical benefits for patients with FGFR2-positive cholangiocarcinoma. Beyond Pemegatinib, Futibatinib, a covalent pan-FGFR inhibitor, has also received regulatory approval for patients with FGFR2 fusion as a positive disease. Although random phase III data are pending, initial evidence indicates similar efficacy, with better tumor control in the later-line treatment settings. These agents strengthen the importance of regular genomic screening, as recent observation studies show that most FGFR2 fusion events are unique to individual patients and require both DNA and RNA-based sequencing to identify [7].

Treatment resistance is still a significant obstacle. In the FIGHT 202 trial and the real-world cohorts, resistance typically emerged after nine months, and ordinary side effects such as hyperphosphatemia, ocular toxicity, nail changes, and fatigue were recorded. According to [28] these toxicities were generally manageable through dose adjustments and supportive care, with serious side effects that occurred in 64 percent of patients in clinical trials, including deadly incidents in 4 percent. Dose reductions were necessary for up to 33 percent of patients in real-world analyses [7]. Parallel to targeted therapy, locoregional modalities are still crucial. Surgical resection provides a potential cure if complete removal is achieved, but still only 20-30 percent of patients have resectable disease. For unresectable intrahepatic tumors, approaches such as photodynamic therapy, radioembolization, and transarterial chemoembolization provide symptomatic relief and modest survival benefits. The integration of systemic chemotherapy regimens, such as gemcitabine plus cisplatin combined with the immunotherapy agent durvalumab in the TOPAZ-1 trial, has provided a significant survival benefit. This regime is now considered standard first-line care.

Diagnostic advances are emerging, where Liquid biopsy using circulating tumor DNA results in greater than 80% sensitivity for detecting FGFR2 fusions with excellent concordance to tissue-based assays [30]. This non-invasive test can accelerate patient identification and enable real-time molecular evolution and resistance tracking. Still, large holes remain. The average time post-diagnosis for molecular profiling is five months, despite guideline recommendations and often delays FGFR-targeted therapy. Clinical trial participation remains limited, more importantly, with less representation of minority or resource-limited populations. Side effect management adds even more complexity since up to 40% of patients need treatment modifications. Surgical options are still minimal because the disease reaches an advanced stage at presentation; apart from that, patients from low-income countries do not have access to molecular diagnostics or targeted treatment options.

4. DISCUSSION

This review highlights significant advances in the understanding and management of cholangiocarcinoma, but several issues require critical evaluation. While molecularly targeted therapies such as FGFR2 and IDH1 inhibitors have shown promising clinical outcomes [21, 22], access to genomic testing remains uneven across regions. In many low- and middle-income countries, molecular profiling is still unavailable, limiting the applicability of precision medicine in routine practice [11].

Conflicting findings exist regarding the prognostic impact of certain molecular markers. For example, some studies suggest improved outcomes for FGFR2 fusion–positive patients [21], while others report limited benefit due to rapid development of acquired resistance [22]. Similarly, although immunotherapy combinations (e.g., durvalumab with chemotherapy) have demonstrated modest survival benefits [23], results across trials remain heterogeneous, reflecting tumor microenvironment complexity.

Diagnostic strategies also remain a point of debate. Traditional biomarkers such as CA19-9 lack sufficient specificity [15], whereas novel approaches like liquid biopsy demonstrate high sensitivity but are not yet validated for widespread clinical use [24]. Integrating these tools into standard diagnostic pathways will require further large-scale, prospective validation.

The clinical implications of these findings are substantial. Precision oncology is shifting the therapeutic landscape, yet treatment resistance, late diagnosis, and socioeconomic disparities continue to hinder progress [11]. Greater efforts are needed to shorten the time from diagnosis to molecular profiling and to expand clinical trial participation, especially among underrepresented populations.

This review has several limitations. As a narrative review, it does not include a systematic risk-of-bias assessment, and the selection of studies may reflect publication availability rather than comprehensive coverage [5]. Furthermore, rapidly emerging data in this field may alter some of the conclusions drawn here.

Future research should address mechanisms of drug resistance, develop cost-effective diagnostic strategies, and ensure equitable access to targeted therapies. Only through a combined effort in translational research, clinical innovation, and health policy can the survival and quality of life of patients with cholangiocarcinoma be significantly improved.

5. CONCLUSIONS

Cholangiocarcinoma is an uncommon but aggressive cancer of the biliary tract, most often diagnosed at advanced stages and associated with poor survival, typically below 20% at five years. Although its incidence is lower than that of other gastrointestinal malignancies, the worldwide burden continues to rise, particularly in areas affected by liver fluke infections and chronic liver disease.

Recent advances in molecular characterization have changed therapeutic possibilities. Targeted agents directed at FGFR2 fusions and IDH1 mutations, along with the introduction of immunotherapy combined with chemotherapy, have provided new treatment opportunities and incremental gains in survival.

Despite these achievements, major obstacles remain, especially unequal access to molecular testing and innovative therapies, the persistence of tumor heterogeneity, and the problem of acquired resistance.

Future progress will require earlier diagnosis, expansion of molecular diagnostics, wider patient inclusion in clinical trials, and health-system strategies that ensure equitable care. Precision oncology is emerging as a realistic path to improved outcomes, but its benefits must be extended more broadly to truly impact patient survival and quality of life.

DISCLOSURES

AUTHOR`S CONTRIBUTION

Conceptualization: Albert Kosarewicz, Patrycja Krysiak

methodology: Michał Wabiszczewicz, Albert Lompart

software: Albert Kosarewicz, Łukasz Woźniak

check: Michał Wabiszczewicz, Łukasz Woźniak

formal analysis: Albert Lompart

investigation: Patrycja Krysiak, Łukasz Woźniak

resources: Michał Wabiszczewicz, Albert Lompart, Albert Kosarewicz

data curation: Łukasz Woźniak

writing - review and editing: Patrycja Krysiak, Albert Kosarewicz, Albert Lompart

supervision: Michał Wabiszczewicz

project administration: Łukasz Woźniak, Patrycja Krysiak

All authors have read and agreed with the published version of the manuscript.

CONFLICT OF INTEREST

The authors deny any conflict of interest.

USE OF AI

ChatGPT was used for language improvement only, with final responsibility assumed by the authors.

REFERENCES

1. Qurashi, M., Vithayathil, M., & Khan, S. A. (2023). Epidemiology of cholangiocarcinoma. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 51(2), 107064. https://doi.org/10.1016/j.ejso.2023.107064
2. Bertuccio, P., Malvezzi, M., Carioli, G., Hashim, D., Boffetta, P., El-Serag, H. B., La Vecchia, C., & Negri, E. (2019). Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. Journal of hepatology, 71(1), 104–114. https://doi.org/10.1016/j.jhep.2019.03.013
3. Didkowska, J., Wojciechowska, U., Barańska, K., Miklewska, M., Michałek, I. M., & Olasek, P. (2023). Nowotwory złośliwe w Polsce w 2021 roku. Krajowy Rejestr Nowotworów, Narodowy Instytut Onkologii – PIB, Warszawa. Available at: https://onkologia.org.pl/sites/default/files/publications/2024-01/0_krn-2023-book-2024-01-22.pdf
4. Pascale, A., Rosmorduc, O., & Duclos-Vallée, J.-C. (2023). New epidemiologic trends in cholangiocarcinoma. Clinics and Research in Hepatology and Gastroenterology, 47(9), 102223. https://doi.org/10.1016/j.clinre.2023.102223
5. Elias, C., Rahman, A., Mial-Anthony, J., Godwin Packiaraj, Crane, A., Sarmad Alshamery, Ganoza, A., Vikraman Gunabushanam, Powers, C., Stalin Dharmayan, Subashini Ayloo, Liu, H., Christof Kaltenmeier, Eishan Ashwat, Neckerman, I., Berkay Demirors, & Molinari, M. (2024). Advancements in cholangiocarcinoma: evolving strategies for diagnosis, treatment, and palliation over three decades. Chinese Clinical Oncology, 13(5), 70–70. https://doi.org/10.21037/cco-23-144
6. Silverman, I. M., Hollebecque, A., Friboulet, L., Owens, S., Newton, R. C., Zhen, H., Féliz, L., Zecchetto, C., Melisi, D., & Burn, T. C. (2021). Clinicogenomic Analysis of FGFR2-Rearranged Cholangiocarcinoma Identifies Correlates of Response and Mechanisms of Resistance to Pemigatinib. Cancer Discovery, 11(2), 326–339. https://doi.org/10.1158/2159-8290.cd-20-0766
7. Parisi, A., Delaunay, B., Giada Pinterpe, Hollebecque, A., Blanc, J. F., Bouattour, M., Assenat, E., Abdelghani, M. B., Sarabi, M., Niger, M., Vivaldi, C., Mandalà, M., Palloni, A., Bensi, M., Silvio Ken Garattini, Tougeron, D., Combe, P., Salati, M., Rimini, M., & Cella, C. A. (2024). Pemigatinib for patients with previously treated, locally advanced or metastatic cholangiocarcinoma harboring FGFR2 fusions or rearrangements: A joint analysis of the French PEMI-BIL and Italian PEMI-REAL cohort studies. European Journal of Cancer, 200, 113587–113587. https://doi.org/10.1016/j.ejca.2024.113587
8. Wang, J., Liu, S., Cao, Y., & Chen, Y. (2024). Overcoming treatment resistance in cholangiocarcinoma: current strategies, challenges, and prospects. Frontiers in Cell and Developmental Biology, 12. https://doi.org/10.3389/fcell.2024.1408852
9. Gad, M. M., Saad, A. M., Faisaluddin, M., Gaman, M. A., Ruhban, I. A., Jazieh, K. A., Al-Husseini, M. J., Simons-Linares, C. R., Sonbol, M. B., & Estfan, B. N. (2020). Epidemiology of Cholangiocarcinoma; United States Incidence and Mortality Trends. Clinics and Research in Hepatology and Gastroenterology, 44(6), 885–893. https://doi.org/10.1016/j.clinre.2020.03.024
10. Sahat, O., Bilheem, S., Lim, A., Kamsa-ard, S., Suwannatrai, A. T., Uadrang, S., Leklob, A., Chansaard, W., Sriket, N., Santong, C., Daoprasert, K., & Kamsa-ard, S. (2025). Updated cholangiocarcinoma incidence trends and projections in Thailand by region based on data from four population-based cancer

registries. The Lancet Regional Health - Southeast Asia, 35, 100569. https://doi.org/10.1016/j.lansea.2025.100569

11. Abioye, O. F., Kaufman, R., Greten, T. F., & Monge, C. (2025). Disparities in Cholangiocarcinoma Research and Trials: Challenges and Opportunities in the United States. JCO Global Oncology, 11. https://doi.org/10.1200/go-24-00537
12. Colyn, L., Alvarez-Sola, G., Latasa, M. U., Uriarte, I., Herranz, J. M., Arechederra, M., Vlachogiannis, G., Rae, C., Pineda-Lucena, A., Casadei-Gardini, A., Pedica, F., Aldrighetti, L., López-López, A., López-Gonzálvez, A., Barbas, C., Ciordia, S., Van Liempd, S. M., Falcón-Pérez, J. M., Urman, J., & Sangro, B. (2022). New molecular mechanisms in cholangiocarcinoma: signals triggering interleukin-6 production in tumor cells and KRAS co-opted epigenetic mediators driving metabolic reprogramming. Journal of Experimental & Clinical Cancer Research, 41(1). https://doi.org/10.1186/s13046-022-02386-2
13. Valery, M., Vasseur, D., Fachinetti, F., Boilève, A., Smolenschi, C., Tarabay, A., Antoun, L., Perret, A., Fuerea, A., Pudlarz, T., Valérie Boige, Hollebecque, A., & Ducreux, M. (2023). Targetable Molecular Alterations in the Treatment of Biliary Tract Cancers: An Overview of the Available Treatments. Cancers, 15(18), 4446–4446. https://doi.org/10.3390/cancers15184446
14. Chen, Z., Song, H., Tang, J., Liu, J., & Xia, L. (2024). New direction: identification of immunoinflammatory subtypes and potential therapeutic targets for cholangiocarcinoma. Discover Oncology, 15(1). https://doi.org/10.1007/s12672-024-01628-3
15. Shin, D. W., Moon, S.-H., & Kim, J. H. (2023). Diagnosis of Cholangiocarcinoma. Diagnostics, 13(2), 233–233. https://doi.org/10.3390/diagnostics13020233
16. Orzan, R. I., Pojoga, C., Agoston, R., Radu Seicean, & Andrada Seicean. (2023). Endoscopic Ultrasound in the Diagnosis of Extrahepatic Cholangiocarcinoma: What Do We Know in 2023? Diagnostics, 13(6), 1023–1023. https://doi.org/10.3390/diagnostics13061023
17. Ito, H., Oba, A., Ono, Y., Sato, T., Inoue, Y., & Takahashi, Y. (2024). Bile liquid biopsy for biliary cancer: a novel diagnostic tool in the era of precision medicine. HPB, 26, S606–S607. https://doi.org/10.1016/j.hpb.2024.04.027
18. Lee, A. J., & Chun, Y. S. (2018). Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. Chinese Clinical Oncology, 7(5), 52–52. https://doi.org/10.21037/cco.2018.07.03
19. Aphivatanasiri, C., Sa-Ngiamwibool, P., Sangkhamanon, S., Intarawichian, P., Kunprom, W., Thanee, M., Prajumwongs, P., Khuntikeo, N., Titapun, A., Jareanrat, A., Thanasukarn, V., Srisuk, T., Luvira, V., Eurboonyanun, K., Promsorn, J., Loilome, W., Wee, A., & Koonmee, S. (2022). Modification of the eighth AJCC/UICC staging system for perihilar cholangiocarcinoma: An alternative pathological staging system from cholangiocarcinoma-prevalent Northeast Thailand. Frontiers in Medicine, 9. https://doi.org/10.3389/fmed.2022.893252
20. Lozada, M. E., Zhang, N., Jin, W., Nicha Wongjarupong, Yang, J. D., Voss, M. M., Kritika Prasai, Amakye, D. O., Harmsen, W. S., Chaudhary, S., Bathe, O. F., Borad, M. J., Patel, T. C., Gores, G. J., Therneau, T. M., & Roberts, L. R. (2023). CS-iCCA, A New Clinically Based Staging System for Intrahepatic Cholangiocarcinoma: Establishment and External Validation. The American Journal of Gastroenterology, 118(12), 2173–2183. https://doi.org/10.14309/ajg.0000000000002258
21. Hadfield, M. J., DeCarli, K., Bash, K., Sun, G., & Almhanna, K. (2023). Current and Emerging Therapeutic Targets for the Treatment of Cholangiocarcinoma: An Updated Review. International Journal of Molecular Sciences, 25(1), 543. https://doi.org/10.3390/ijms25010543
22. LaPelusa, M., Heumann, T., Goff, L., & Agarwal, R. (2023). Targeted therapies in advanced biliary tract cancers—a narrative review. Chinese Clinical Oncology, 12(2), 14–14. https://doi.org/10.21037/cco-22-93
23. Shi, G., Huang, X., Wen, T., Song, T., Kuang, M., Mou, H., Bao, L., Zhao, H., Zhao, H., Feng, X., Zhang, B., Peng, T., Zhang, Y., Li, X., Yu, H., Cao, Y., Liu, L., Zhang, T., Wang, W., & Ran, J. (2022). Pemigatinib in previously treated Chinese patients with locally advanced or metastatic cholangiocarcinoma carrying FGFR2 fusions or rearrangements: A phase II study. Cancer Medicine, 12(4), 4137–4146. https://doi.org/10.1002/cam4.5273
24. Jones, L., Starling, N., & Chau, I. (2024). Making a Path for Liquid Biopsy as a Supplementary Diagnostic Tool in Advanced Biliary Tract Cancers. Default Digital Object Group. https://doi.org/10.1200/adn.24.201649
25. Cadamuro, M., Al-Taee, A., & Gonda, T. A. (2023). Advanced endoscopy meets molecular diagnosis of cholangiocarcinoma. Journal of Hepatology, 78(5), 1063–1072. https://doi.org/10.1016/j.jhep.2023.01.027
26. Zhang, R., Puzzoni, M., Mariani, S., Zheng, Y., Liscia, N., Guo, Y., Donisi, C., Liu, Y., Valentino Impera, Fang, W., & Scartozzi, M. (2021). Emerging treatment evolutions and integrated molecular

characteristics of biliary tract cancers. Cancer Science, 112(12), 4819–4833. https://doi.org/10.1111/cas.15139

27. Soulier, M., Lekbaby, B., Houari, I., Decauchy, H., Pavy, A., Coumes, A., Morichon, R., Dufour, T., Fouassier, L. (2024). Targeting Cholangiocarcinoma Cells By Cold Piezoelectric Plasmas: In Vitro Efficacy And Cellular Mechanisms. https://doi.org/10.48550/arXiv.2412.09761
28. Patel, T. H., Marcus, L., M. Naomi Horiba, Donoghue, M., Chatterjee, S., Mishra-Kalyani, P. S., Schuck, R. N., Li, Y., Zhang, X., Zirkelbach, J. F., Rosane Charlab, Liu, J., Yang, Y., Lemery, S. J., Pazdur, R., Theoret, M. R., & Fashoyin-Aje, L. A. (2022). FDA Approval Summary: Pemigatinib for Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma with FGFR2 Fusion or Other Rearrangement. Clinical Cancer Research, 29(5), 838–842. https://doi.org/10.1158/1078-0432.ccr-22-2036
29. Saverno, K., Zimmerman, K. M., Cherrishe Brown-Bickerstaff, Kotomale, A., Rodriguez, M., Feinberg, B., Ren, H., Blecker, M., & Kim, R. (2024). Real-world use of pemigatinib for the treatment of cholangiocarcinoma in the US. The Oncologist, 30(1). https://doi.org/10.1093/oncolo/oyae204
30. Borad, M. J., Conner, T., He, L., Reza Kazerooni, Salimi, T., & Epstein, R. S. (2022). Real-world genomic testing, treatment, and outcomes in patients with cholangiocarcinoma with FGFR2 fusions/rearrangements. Journal of Clinical Oncology, 40(16_suppl), e16168–e16168. https://doi.org/10.1200/jco.2022.40.16_suppl.e16168

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