# Cholangiocarcinoma in Latin America: a multicentre observational study alerts on ethnic disparities in tumour presentation and outcomes

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## Summary

**Background** Cholangiocarcinoma (CCA) represents a global health challenge, with rising incidence and mortality rates. This study aimed to elucidate the clinical course and practices of CCA in Latin America.

**Methods** This observational cohort study investigated individuals diagnosed with CCA between 2010 and 2023 at five referral centres across Latin America. Demographic, biochemical, and clinical data were analysed.

**Findings** A total of 309 patients were enrolled, demonstrating a balanced distribution of CCA subtypes (intrahepatic, perihilar, and distal), with Hispanics and Caucasians as the predominant ethnic groups, followed by Africans. Major risk factors identified included age, diabetes, obesity, MASLD, bile duct stones, and cholecystitis. Disparities in overweight/obesity prevalence were noted among CCA subtypes and ethnicities, with higher rates in extrahepatic CCA and among Hispanics and Caucasians. At diagnosis, 72% of patients had ECOG-PS scores of 0–1, with disease presentations ranging from localized (47%) to locally advanced (19%) and metastatic (34%). Patients who did not receive any anti-cancer therapy exhibited a median survival of 2.3 months. Survival rates significantly improved across treatment modalities, with surgery yielding the longest (34 months), followed by chemotherapy (8 months). Notably, Africans presented with worse ECOG-PS scores and more advanced disease, while Hispanics were less

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frequently treated with chemotherapy for advanced disease, contributing to lower survival rates (8.3 and 6 months, respectively) compared to Caucasians (12.6 months).

**Interpretation** The high prevalence of late-stage CCA diagnosis in Latin America, particularly among individuals of African ethnicity, coupled with a significant proportion of Hispanic patients not receiving chemotherapy, underscores the dismal prognosis for these patients. These findings reveal structural challenges in cancer screening and healthcare access among diverse ethnic backgrounds and lower socioeconomic statuses in the region. Urgent measures are needed, including the identification of preventable risk factors, raising awareness among high-risk populations, and establishing equitable health coverage to address these disparities.

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**Keywords:** Biliary cancer; Ethnicities; Subtypes; Risk factors; Management

## Research in context

### Evidence before this study

The incidence and associated mortality of cholangiocarcinoma (CCA) have significantly increased globally over recent decades, with East Asia reporting notably higher rates than Western countries. While increased disease awareness and advancements in diagnostics may partially explain this trend, data indicate a genuine rise in cases. Our literature search in PubMed, using terms such as "cholangiocarcinoma," "biliary cancer," "risk factors," and "treatment," revealed a predominant research focus on Western populations, leaving a dearth of data from other regions, particularly Latin America. Existing studies highlight a wide range of risk factors, including chronic biliary diseases, viral hepatitis, and liver fluke infections, which exhibit significant geographic variability. Despite the presence of some large multicentre studies in Europe, the lack of data from Latin America represents a critical gap in our understanding of CCA presentation, risk profiles, and outcomes across diverse populations. In 2019, the European-South American Consortium to Assess Liver-Originated Neoplasia (ESCALON) secured a Horizon EU 2020 grant to address this gap by developing cost-effective diagnostic tools for hepatobiliary cancers and establishing the Latin American Cholangiocarcinoma (LATAM-CCA) Registry. This study aims to utilize data from the LATAM-CCA Registry to examine the natural course of CCA within the first multicentre Latin American (LATAM) cohort, with the goal of informing targeted healthcare strategies both regionally and globally.

### Added value of this study

After five years of collaborative efforts (2019–2024), the LATAM-CCA Registry has produced the first comprehensive evaluation of CCA in Latin America. This analysis represents a major milestone in international cooperation, leveraging the expertise of institutions dedicated to CCA research and management. The study explores diverse aspects of CCA, encompassing clinical presentation, risk factors, management approaches, outcomes, and ethnic diversity within the region, among others. Importantly, the results highlight the importance of early CCA detection and uncover concerning disparities in survival rates among ethnic groups, emphasizing the urgent need for new public health strategies.

### Implications of all the available evidence

The study's findings highlight the high prevalence of late-stage CCA diagnosis in Latin America, leading to generally poor prognosis, and highlight structural obstacles in cancer screening and healthcare accessibility across diverse ethnic and socioeconomic groups. Urgent actions are identified, including education on risk factors and symptoms, raising awareness among high-risk populations, and ensuring equitable healthcare access and coverage to enhance early detection and treatment adherence. Moreover, the study emphasizes the importance of greater representation of the Latin American population in clinical trials and the strengthening of multicentric databases. These efforts are crucial for improving outcomes and advancing the treatment of CCA patients in the region.

## Introduction

Cholangiocarcinoma (CCA) comprises a wide spectrum of bile duct cancers. Over recent decades, there has been a marked global rise in both the incidence and mortality rates associated with CCA.[1,2] This increase is likely attributed to heightened disease awareness, improved diagnostic capabilities, and a genuine rise in the number of cases.[3,4] Regions in East Asia notably exhibit higher rates compared to Western nations,[1,2] highlighting the urgent need to explore associated risk

factors, epidemiological trends, and treatment accessibility.

The International Classification of Diseases 11th Edition (ICD-11), published in 2022, categorises CCAs anatomically into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA).[5] Each subtype is linked to specific risk factors, molecular profiles, clinical presentations, and outcomes.[6,7] Despite advances, the prognosis of patients with CCA remains poor due to late-stage cancer detection and the limited effectiveness of current systemic treatments.[7,8]

While the aetiology of most CCAs remains elusive, certain factors significantly increase the risk of biliary cancer development. These include the presence of choledochal cysts, cholelithiasis, chronic biliary conditions like primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC), viral hepatitis, cirrhosis, and liver fluke infestations (such as *Opisthorchis viverrini* and *Clonorchis sinensis*), which are prevalent in certain South Asian regions contributing to their high CCA incidence.[6,7,9] Additionally, lesser-explored factors such as metabolic comorbidities like obesity and diabetes, which are widespread, have been recently associated with CCA development.[10]

The variability of these factors across regions, along with ethnic and socioeconomic disparities, highlights the importance of understanding region-specific risk conditions. While a European multicentric study has illuminated aspects of CCA presentation, progression, and outcomes,[7] data from other regions, particularly Latin America, remain scarce.[11,12] Furthermore, global clinical trials often lack diverse representation. International collaboration is crucial for comprehensively examining the global CCA landscape, identifying challenges for future research and actions. This study aims to bridge this gap by investigating the natural course of CCA within the first international multicentric Latin American (LATAM) cohort.

## Methods

### Patient recruitment and data collection

The Latin American Cholangiocarcinoma (LATAM-CCA) Registry is a multicentre observational cohort study that includes patients with a confirmed diagnosis of CCA by histology or those with radiological findings highly suggestive of CCA. The study collects information on demographics, risk factors, biochemical parameters, diagnostic and tumour-associated features, as well as treatment data. The LATAM cohort comprises patients diagnosed with CCA, recruited retrospectively from 2010 to 2019 and prospectively until 2023.

Relevant data were retrieved from medical records with contributions from members of the European-South American Consortium to Assess Liver-Originated Neoplasia (ESCALON project; https://escalon.eu), selected due to their recognition as regional referents in CCA management. These centres were chosen for their multidisciplinary teams with expertise in CCA care and their commitment to upholding ethical and scientific standards in the design, recording, and reporting of data. The LATAM-CCA Registry encompasses five referral centres across five Latin American countries: Argentina, Brazil, Chile, Ecuador, and Peru. Although two of the hospitals (located in Chile and Argentina) are private clinics, all institutions serve a diverse population ranging from low to high income. Additionally, two of the sites (in Chile and Brazil) are specialized oncological centres, while the remaining three are tertiary hospitals. Each hospital is involved in patient recruitment and specializes in different areas of oncology and related fields, ensuring a broad representation of clinical practices and patient demographics. Importantly, all five centres have access to the full spectrum of standard treatments for CCA, including surgical approaches, chemotherapy, and radiotherapy. This wide availability of treatments is crucial to ensuring that the study results are not biased by disparities in treatment options.

The study protocol was approved by the Ethics Committee of the coordinating centre (Donostia University Hospital, San Sebastian, Spain), and each participating centre obtained local ethical approval (or equivalent). Informed consent was obtained from patients for prospective data collection, while for retrospective data collection, consent was waived when approved by the local Ethics Committee.

### Data deposition

The LATAM-CCA Registry utilizes the REDCap (Research Electronic Data Capture) tool for data collection and management, hosted at the *Asociación Española de Gastroenterología* (AEG; www.aegastro.es).[13,14] REDCap is a secure, web-based software platform designed to facilitate data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails to track data manipulation and export procedures; 3) automated export procedures for seamless data downloads to standard statistical packages; and 4) procedures for data integration and interoperability with external sources.

### Data analysis

Data export was conducted in July 2023, followed by data harmonization and completeness checks. Patients lacking mandatory epidemiological and/or clinical data were excluded. Patients were classified based on the anatomical location of the primary tumour within the bile ducts according to ICD-11 criteria and the expertise of investigators within multidisciplinary teams, as either intrahepatic (2C12), perihilar (2C18), or distal (2C15). Next, the cohort was sorted based on ethnicity, defined following National Institutes of Health guidance,[15,16] and was determined based on self-identification or information from medical notes. Of note, due to the small

sample size in the Asian ethnic group (n = 4), these individuals were excluded from the sub-analyses. Positive regional lymph node invasion and/or metastasis were identified through imaging techniques and, when possible, histology. Regional invasion was radiologically defined as regional lymph node tumour invasion measuring above 1.5 cm in diameter (short axis), classified as N positive according to the American Joint Committee on Cancer. Metastatic disease indicated distant involvement, except for liver dissemination of iCCA, which is currently classified as multiple tumours (T2b). Based on local multidisciplinary team discussions, patients were divided into two groups: those with resectable *vs.* unresectable CCA, following widely accepted international guidelines.[17,18] Accordingly, treatments were categorized as follows: 1) surgery (including tumour resection or liver transplantation subdivided into resection margin R0 [negative margin tumour resection] and R1 [microscopic residual disease]); 2) chemotherapy; and 3) best supportive care encompassing those without any anti-cancer treatment. Patients undergoing palliative or exploratory surgery were classified according to the subsequent therapeutic regimen. Additionally, only three patients received locoregional therapies, which were consequently excluded from the treatment-related analyses.

### Statistical analysis

Baseline demographics and risk factors were summarized using descriptive statistics. Continuous data were presented as median and interquartile range (IQR), while categorical variables were summarized as frequency and percentage (n, %). Probability calculations excluded cases with unknown information.

For multiple comparisons, non-parametric data were compared using Kruskal–Wallis tests, followed by the Dunn-Bonferroni *post hoc* method for pairwise comparisons. Pearson's chi-square test was used to compare categorical variables between subgroups, with post hoc analysis conducted using the Z-test to identify differences between specific groups. Bonferroni correction was applied to adjust *p*-values obtained in these comparisons to control Type I error.

Overall survival (OS) was assessed as the time from diagnosis to death or last medical visit, while post-treatment survival considered the treatment start date. Patients with no information on survival, lost to follow-up, or alive at the last medical visit were censored at the date of the latest record. Patients alive at the last medical visit, with less than 1 year of follow-up from their CCA diagnosis, were excluded from the survival analyses. Survival analysis was performed using the Kaplan–Meier method and Cox regression. The log-rank test was used to compare survival rates in Kaplan–Meier curves. Prognostic factors were analysed in terms of hazard ratio (HR), 95% confidence intervals (95% CIs), and *p*-values. The proportional hazards assumption in the Cox regression model was tested to evaluate the effect of the ethnic group on survival while controlling for the country of origin.

Statistical analyses were conducted using IBM SPSS Statistics Version 29.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.0 (GraphPad Software, La Jolla, California, USA).

### Role of funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or manuscript preparation. The researchers maintained complete independence in conducting the study and reporting its findings.

## Results

### Cholangiocarcinoma-related risk factors

The study initially enrolled 317 patients from five Latin American countries. After applying the inclusion criteria, 309 patients were considered eligible, with 97 (31.4%) diagnosed with iCCA, 99 (32.0%) with pCCA, and 113 (36.6%) with dCCA. Exclusions were made for the following reasons: undefined site of origin (n = 5), mixed iCCA and HCC phenotype (n = 2), and unknown diagnosis date (n = 1; Supplementary Fig. S1). At the time of diagnosis, the median age was 64.1 years (IQR: 57–72), consistent across all CCA subtypes. Notably, 52% of patients were diagnosed between the ages of 40 and 64, with 30% falling within the 65–74 age range. Additionally, a higher proportion of affected women was observed, revealing distinct sex distribution patterns among CCA subtypes: iCCA (62.9%), pCCA (52.5%), and dCCA (47.8%), with the latter showing higher male preponderance (Table 1).

Regarding comorbidities, the study population showed a median body mass index (BMI) of 24.8 kg/m$^2$, with a significantly lower prevalence of overweight/obesity (BMI ≥25 kg/m$^2$) among patients with iCCA (36%) compared to pCCA (54%), and dCCA (51%). Other metabolic-associated risk factors were prevalent across subtypes, including diabetes (18.5%), dyslipidaemia (9.9%), and metabolic dysfunction-associated steatotic liver disease (MASLD, 10.1%). Moreover, 3 patients (1%) were diagnosed with PSC. Prior episodes of cholecystitis were present in 7.7% of patients, while bile duct stones were reported in 8.7%. In terms of liver-related diseases, 6 patients (2.1%) had viral hepatitis (including hepatitis B and/or C), and only 2 (0.7%) had cirrhosis. In this context, 12.1% of patients had a history of high alcohol consumption, and 29.6% of smoking (Table 1).

### Clinical and pathological presentation of CCA

Most patients presented with ECOG-PS scores of 0–1 (71.9%), with significant variations across subtypes: iCCA (60.0%), pCCA (69.7%), and dCCA (84.4%)

| Characteristic | Total (n = 309) | iCCA (n = 97) | pCCA (n = 99) | dCCA (n = 113) | *p* value |
|---|---|---|---|---|---|
| Age, median (IQR) | 64.1 (56.7–72.1) | 63.0 (55.1–68.2) | 64.7 (58.3–73.8) | 63.6 (57.4–72.4) | 0.773 |
| 18–39 | 7 (2.3) | 3 (3.1) | 2 (2.0) | 2 (1.8) | 0.655 |
| 40–64 | 160 (51.8) | 53 (54.6) | 49 (49.5) | 58 (51.3) | |
| 65–74 | 92 (29.8) | 31 (32.0) | 28 (28.3) | 33 (29.2) | |
| ≥75 | 50 (16.2) | 10 (10.3) | 20 (20.2) | 20 (17.7) | |
| Sex, n (%) | | | | | |
| Male | 142 (46.0) | 36 (37.1)$_a$ | 47 (47.5)$_{ab}$ | 59 (52.2)$_b$ | 0.085 |
| Female | 167 (54.0) | 61 (62.9)$_a$ | 52 (52.5)$_{ab}$ | 54 (47.8)$_b$ | |
| BMI, median (IQR) | 24.8 (21.8–27.5) | 24.0 (20.8–26.5) | 25.3 (22.1–28.3) | 25.1 (22.1–27.6) | **<0.05** |
| BMI ≥ 25 | 131 (32.1) | 32 (36.0)$_a$ | 46 (53.5)$_b$ | 53 (50.5)$_b$ | **<0.05** |
| Diabetes, n (%) | 56 (18.5) | 20 (20.8) | 14 (14.4) | 22 (20.2) | 0.447 |
| MASLD, n (%) | 30 (10.1) | 7 (7.4) | 9 (9.5) | 14 (13.1) | 0.530 |
| Dyslipidaemia, n (%) | 30 (9.9) | 10 (10.4) | 9 (9.2) | 11 (10.0) | 0.958 |
| Arterial Hypertension, n (%) | 116 (38.2) | 31 (32.3) | 45 (45.9) | 40 (36.4) | 0.132 |
| Ex + Regular smoker, n (%) | 88 (29.6) | 26 (27.4) | 31 (32.3) | 31 (29.2) | 0.753 |
| Ex + Regular drinker, n (%) | 36 (12.1) | 12 (12.6) | 8 (8.3) | 16 (15.1) | 0.334 |
| Biliary conditions, n (%) | | | | | |
| Bile duct stones | 26 (8.7) | 5 (5.3) | 11 (11.3) | 10 (9.3) | 0.314 |
| Cholecystitis | 23 (7.7) | 10 (10.5) | 4 (4.1) | 9 (8.3) | 0.236 |
| PSC | 3 (1.0) | 2 (2.1) | 1 (1.0) | 0 (0.0) | 0.322 |
| IBD (UC) | 1 (0.3) | 0 (0.0) | 1 (1.0) | 0 (0.0) | 0.350 |
| Liver diseases, n (%) | | | | | |
| Viral hepatitis | 6 (2.1) | 3 (3.3) | 2 (2.2) | 1 (0.9) | 0.508 |
| Cirrhosis | 2 (0.7) | 1 (1.1) | 1 (1.0) | 0 (0.0) | 0.568 |

BMI, body mass index; dCCA, distal cholangiocarcinoma; IBD, inflammatory bowel disease; iCCA, intrahepatic cholangiocarcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; pCCA, perihilar cholangiocarcinoma; PSC, primary sclerosing cholangitis; UC, ulcerative colitis. *Missing values*: BMI = 29; Diabetes = 7; MASLD = 13; Dyslipidaemia = 5; Arterial hypertension = 5; Smoking = 12; Alcohol abuse = 12; Biliary conditions = 9; Viral hepatitis = 17; Cirrhosis = 9. Statistical analyses: One-way ANOVA and Kruskal–Wallis tests for continuous variables, and Pearson's Chi-square test for categorical variables were performed by comparing the three CCA subtypes (iCCA *vs.* pCCA *vs.* dCCA). Different letters in the subscript indicate significant differences between CCA subtypes ($p < 0.05$; a *vs.* b indicates differences, but not *vs.* ab). Bold indicates significant *p*-values ($p < 0.05$).

***Table 1:*** **Frequency of risk factors in the study population and their association with CCA subtypes.**

(Table 2). The serum tumour markers carbohydrate antigen 19-9 (CA19-9) and carcinogenic embryonic antigen (CEA), commonly analysed to aid in CCA diagnosis, exhibited elevated levels in 77.3% and 46.9% of patients, respectively. Notably, dCCA demonstrated lower frequencies of CA19.9 and CEA elevation compared to iCCA and pCCA. Conversely, elevated levels of both CA19-9 and CEA were significantly associated with the presence of distant metastasis at the time of diagnosis, with odds ratios of 2.22 (95%CI: 1.10–4.50) and 1.86 (95%CI: 1.05–3.30), respectively (Supplementary Fig. S2).

At diagnosis, 47.2% had localised disease, 18.8% had locally advanced disease with regional nodal invasion, and 34.0% had distant organ metastasis (Table 2). Remarkably, iCCAs were more likely to present with metastasis (48.3%) compared to other subtypes, whereas dCCAs were identified as the least invasive CCA subtype (21.0%). Multifocal tumours were observed in 22.6% of cases, predominantly in patients with iCCA, showing a frequency of 45.3%. The most prevalent growth pattern was mass-forming (56.2%), followed by periductal infiltrating (28.3%) and intraductal growing (19.5%). Mass-forming was predominant in iCCA (90.8%), while periductal infiltrating was more common in pCCA (56.6%). In dCCA, both intraductal growth and mass-forming patterns were common (39.8% and 43.2%, respectively).

### Ethnic disparities in risk factors, tumour presentation, and outcome for patients with CCA

Given the rich ethnic diversity within Latin America, an extensive analysis was conducted across Caucasians, Hispanics, and Africans. While numerous risk factors associated with CCA appeared consistent across ethnicities, distinct race-related factors were identified. Particularly, Africans exhibited lower BMI at diagnosis compared to the other ethnicities, corresponding with a reduced prevalence of overweight/obesity: Africans (28.9%), Caucasians (49.6%), and Hispanics (51.2%) (Table 3). Conversely, a positive association was observed between the history of cholecystitis and ethnicity, with a lower frequency among Caucasians and a higher occurrence among Hispanics.

In terms of tumour presentation, an intriguing association was observed between ethnicity and the

| Characteristic | Total (n = 309) | iCCA (n = 97) | pCCA (n = 99) | dCCA (n = 113) | p value |
|---|---|---|---|---|---|
| ECOG-PS, n (%) | | | | | |
| 0–1 | 218 (71.9) | 57 (60.0)$_a$ | 69 (69.7)$_a$ | 92 (84.4)$_b$ | **<0.001** |
| ≥2 | 85 (28.1) | 38 (40.0)$_a$ | 30 (30.3)$_a$ | 17 (15.6)$_b$ | |
| Tumour markers, median (IQR) | | | | | |
| CA19-9 | 150.4 (44.1–675.3) | 157.6 (46.9–578.3) | 202.4 (69.8–1503.8) | 134.0 (25.8–384.8) | 0.325 |
| ≥37 UI/mL | 221 (77.3) | 71 (78.9)$_{ab}$ | 76 (84.4)$_b$ | 74 (69.8)$_a$ | **<0.05** |
| CEA | 4.6 (2.1–15.4) | 5.4 (2.2–34.0)$_a$ | 5.5 (2.4–17.8)$_a$ | 3.2 (1.9–6.5)$_b$ | **<0.01** |
| ≥5 ng/mL | 119 (46.9) | 47 (52.8)$_a$ | 44 (56.4)$_a$ | 28 (32.2)$_b$ | **<0.01** |
| Stage at diagnosis, n (%) | | | | | |
| Localized | 133 (47.2) | 30 (32.3)$_a$ | 39 (43.8)$_a$ | 64 (64.0)$_b$ | |
| Regional invasion | 53 (18.8) | 18 (19.4) | 20 (22.5) | 15 (15.0) | **0.001** |
| Distant metastasis | 96 (34.0) | 45 (48.4)$_a$ | 30 (33.7)$_b$ | 21 (21.0)$_c$ | |
| Primary tumour lesions, n (%) | | | | | |
| Single lesion | 216 (77.4) | 52 (54.7)$_a$ | 86 (92.5)$_b$ | 78 (85.7)$_b$ | **<0.0001** |
| Multiple lesions | 63 (22.6) | 43 (45.3)$_a$ | 7 (7.5)$_b$ | 13 (14.3)$_b$ | |
| Pattern of growth, n (%) | | | | | |
| Mass-forming | 141 (56.2) | 79 (90.8)$_a$ | 24 (31.6)$_b$ | 38 (43.2)$_b$ | |
| Periductal infiltrating | 71 (28.3) | 7 (8.0)$_a$ | 43 (56.6)$_b$ | 21 (23.9)$_c$ | **<0.0001** |
| Intraductal growth | 49 (19.5) | 2 (2.3)$_a$ | 12 (15.8)$_b$ | 35 (39.8)$_c$ | |

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; dCCA, distal cholangiocarcinoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma. *Missing values:* ECOG-PS = 6; CA19.9 = 23; CEA = 55; Pattern of growth = 58; Tumour lesions = 30; Stage at diagnosis = 27. Statistical analyses: One-way ANOVA and Kruskal–Wallis tests for continuous variables, and Pearson's Chi-square test for categorical variables were performed by comparing the three CCA subtypes (iCCA *vs.* pCCA *vs.* dCCA). Different letters in the subscript indicate significant differences between CCA subtypes ($p < 0.05$; a *vs.* b, a *vs.* c, b *vs.* c indicates differences; a and b are not different from ab). Bold indicates significant *p*-values ($p < 0.05$).

***Table 2:*** **Clinical and histopathological characteristics associated with CCA tumours.**

anatomical location of CCA (Table 4). Caucasians displayed a higher frequency of dCCA and lower rates of iCCA, in contrast to Hispanics and Africans. Assessing patients' clinical performance at diagnosis using the ECOG-PS scale revealed significant differences among ethnic groups. Notably, African individuals were more frequently functionally limited (ECOG-PS ≥ 2, 49.9%), whereas most Caucasians presented ECOG-PS 0–1 (82.2%). These findings were in line with differences in disease stage between ethnic groups, where Africans presented a greater frequency of metastatic disease, contrasting with Caucasians and Hispanics who displayed lower occurrence. Furthermore, the presence of multifocal disease was predominantly observed among Africans compared to Caucasians, while Hispanics did not exhibit significant differences compared to either group. Importantly, despite some significant differences in the frequency of diagnostic routes across ethnic groups, all demographic segments had equal access to the same radiological and pathological modalities. Therefore, fair and equitable diagnostic modalities were employed among individuals of diverse ethnic backgrounds in this cohort (Supplementary Table S1).

Caucasians demonstrated the longest median overall survival (OS) with 12.6 months (IQR: 34.0–5.4). In contrast, Hispanics and Africans had significantly shorter median OS, with 6.0 months (IQR: 15.8–1.8) and 8.3 months (IQR: 20.9–3.9), respectively. Both Hispanics and Africans showed increased risks of death compared to Caucasians, with Hispanics showing a hazard ratio (HR) of 1.72 (95% CI: 1.26–2.36) and Africans a HR of 1.73 (95% CI: 1.09–2.75) (Fig. 1). These findings highlight disparities in survival among different ethnic groups, regardless of recruitment site or country.

### Therapeutic management and outcomes of patients with CCA

Patients were treated according to local policies and standards of care, as shown in the flowchart outlining the initial therapeutic approach (Fig. 2). Among the 276 patients examined, 80 (29.0%) underwent surgical resection, with the majority achieving R0 resection (24.6%). Notably, a significant proportion of surgical cases were Caucasians (47.3%), which was higher compared to Hispanics (16.8%) and Africans (16.2%) (Supplementary Table S2). Adjuvant treatment post-surgery was relatively uncommon, with only 32.5% of patients receiving any form of post-operative chemotherapy, predominantly gemcitabine or capecitabine (Fig. 2). Overall, 54.9% of patients experienced tumour relapse, with a median relapse-free survival of 10.7 months (IQR: 3.7–18.8). The relative rates of relapse-free survival at 1- and 3-years were 47.2% and 5.6%, respectively (Fig. 2). The median post-treatment survival for patients undergoing tumour resection was

| Characteristic | Caucasian (n = 118) | Hispanic (n = 149) | African (n = 38) | p value |
|---|---|---|---|---|
| Age, median (IQR) | 64.9 (57.4–73.0) | 63.8 (56.7–72.5) | 62.9 (56.3–68.7) | 0.534 |
| 18–39 | 3 (2.5) | 3 (2.0) | 1 (2.6) | 0.537 |
| 40–64 | 56 (47.5) | 78 (52.3) | 24 (63.2) | |
| 65–74 | 37 (31.4) | 42 (28.2) | 11 (28.9) | |
| ≥75 | 22 (18.6)$_a$ | 26 (17.4)$_{ab}$ | 2 (5.3)$_b$ | |
| Sex, n (%) | | | | |
| Male | 59 (50.0) | 64 (43.0) | 16 (42.1) | 0.466 |
| Female | 59 (50.0) | 85 (57.0) | 22 (57.9) | |
| BMI, median (IQR) | 25.0 (22.0–27.5)$_a$ | 25.2 (22.5–27.7)$_a$ | 22.2 (19.6–26.3)$_b$ | **<0.05** |
| BMI ≥ 25 | 58 (49.6)$_a$ | 62 (51.2)$_a$ | 11 (28.9)$_b$ | **<0.05** |
| Diabetes, n (%) | 26 (22.0) | 26 (18.2) | 4 (10.5) | 0.279 |
| MASLD, n (%) | 12 (10.3) | 14 (10.2) | 4 (10.5) | 0.966 |
| Dyslipidaemia, n (%) | 16 (13.7) | 10 (6.9) | 4 (10.5) | 0.190 |
| Arterial Hypertension, n (%) | 50 (42.7) | 48 (33.1) | 16 (42.1) | 0.239 |
| Ex + Regular smoker, n (%) | 42 (36.8)$_a$ | 24 (17.0)$_b$ | 20 (52.6)$_a$ | **<0.0001** |
| Ex + Regular drinker, n (%) | 20 (17.5)$_a$ | 12 (8.5)$_b$ | 4 (10.5)$_{ab}$ | 0.086 |
| Biliary conditions, n (%) | | | | |
| PSC | 1 (0.9) | 1 (0.7) | 1 (2.7) | 0.543 |
| IBD (UC) | 1 (0.9) | 0 (0.0) | 0 (0.0) | 0.454 |
| Cholecystitis | 2 (1.7)$_a$ | 19 (13.2)$_b$ | 2 (5.4)$_{ab}$ | **<0.01** |
| Bile duct stones | 7 (6.1) | 18 (12.5) | 1 (2.7) | 0.073 |
| Chronic liver disease, n (%) | | | | |
| Viral hepatitis | 2 (1.7) | 3 (2.3) | 1 (2.6) | 0.925 |
| Cirrhosis | 0 (0.0) | 1 (0.7) | 1 (2.7) | 0.218 |

BMI, body mass index; IBD, inflammatory bowel disease; MASLD, metabolic dysfunction-associated steatotic liver disease; PSC, primary sclerosing cholangitis; UC, ulcerative colitis. *Missing values*: BMI = 29; Diabetes = 6; MASLD = 12; Dyslipidaemia = 5; Arterial hypertension = 5; Smoking = 12; Alcohol abuse = 12; Biliary conditions = 9; Viral hepatitis = 17; Cirrhosis = 9. *Statistical analyses*: One-way ANOVA and Kruskal–Wallis tests for continuous variables, and Pearson's Chi-square test for categorical variables were performed by comparing the three Ethnic groups. Different letters in the subscript indicate significant differences between Ethnic groups ($p < 0.05$; a *vs.* b indicates differences, but not from ab). Bold indicates significant p-values ($p < 0.05$).

***Table 3*: Ethnic disparities in CCA risk factors.**

33.7 months (IQR: 12.9–57.1), with a 1- and 3-year survival rates of 76.7% and 40.7%, respectively (Fig. 3). Positive lymph node invasion was found in 36.4% of patients, and the median survival for node-positive patients was 21.9 months (IQR: 13.1–40.0) compared to 35.6 months (IQR: 12.6–69.6) for node-negative patients (HR: 1.59; 95%CI: 0.82–3.08) (Supplementary Fig. S3).

Chemotherapy was administered to 110 (39.9%) patients. The most commonly used regimen was gemcitabine plus cisplatin (83.6%), followed by gemcitabine plus oxaliplatin (6.4%) and gemcitabine monotherapy (4.5%) (Fig. 2). In contrast to the findings on tumour resection, Africans received active palliative chemotherapy as the first-line treatment at a higher rate (67.6%) compared to Caucasians (36.4%) and Hispanics (33.6%). However, the choice of regimen did not exhibit ethnicity-related disparities (Supplementary Table S2). Following first-line chemotherapy, 23.4% of patients exhibited a partial response, while 27.1% showed no response, and 31.8% experienced disease progression based on radiological assessments (Fig. 2). Over time, tumour progression after chemotherapy occurred in 65.5% of patients, with a median progression-free survival of 4.2 months (IQR: 2.4–6.9). The relative progression-free survival rates at 6 months declined from 31.4% to 8.6% at 1 year (Fig. 2). The median survival for patients receiving chemotherapy was 8.3 months (IQR: 5.2–13.4), with a 1- and 3-year survival rate of 32.4% and 2.2%, respectively (Fig. 3).

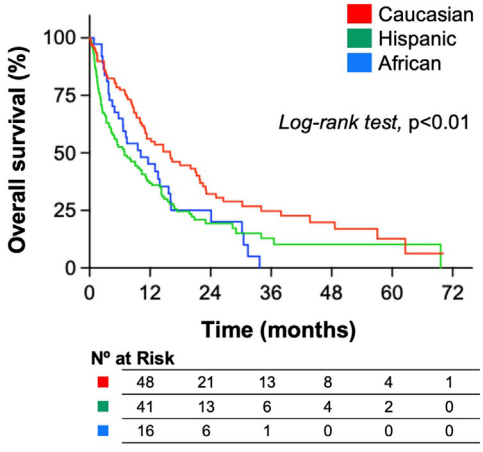
Best supportive care was the primary approach for 31.2% of patients, with a median survival of 2.3 months (IQR: 1.1–5.4; Fig. 2; Fig. 3). Only 20.8% of these patients survived beyond 6 months from their CCA diagnosis (Fig. 3). Of note, an association was also observed in this treatment group with ethnicity, with higher frequency in Hispanics (49.6%), compared to Caucasians (16.4%) and Africans (16.2%; Supplementary Table S2).

For patients who received any form of treatment, no significant differences were observed in post-treatment outcomes across ethnic subgroups. Among patients who underwent surgery, there were no substantial differences in post-treatment outcomes across ethnic groups, with median OS values of 22.5 months (IQR: 9.6–57.1) for Caucasians, 36.6 months (IQR: 18.6–69.6) for Hispanics, and 33.7 months (IQR: 11.6–33.7) for

| Characteristic | Caucasian (n = 118) | Hispanic (n = 149) | African (n = 38) | *p* value |
|---|---|---|---|---|
| CCA subtype, n (%) | | | | |
| Intrahepatic | 23 (19.5)$_a$ | 58 (38.9)$_b$ | 15 (39.5)$_b$ | |
| Perihilar | 38 (32.2) | 46 (30.9) | 13 (34.2) | **<0.01** |
| Distal | 57 (48.3)$_a$ | 45 (30.2)$_b$ | 10 (26.3)$_b$ | |
| ECOG-PS, n (%) | | | | |
| 0–1 | 97 (82.2)$_a$ | 98 (68.5)$_b$ | 19 (50.0)$_c$ | **<0.0001** |
| ≥2 | 21 (17.8)$_a$ | 45 (31.5)$_b$ | 19 (50.0)$_c$ | |
| Tumour markers, median (IQR) | | | | |
| CA19-9 | 147.4 (39.8–605.5) | 162.9 (48.0–831.5) | 145.0 (36.3–861.0) | 0.770 |
| ≥37 UI/mL | 86 (76.8) | 103 (77.4) | 28 (75.7) | 0.973 |
| CEA | 3.6 (2.0–11.4) | 5.0 (2.25–17.4) | 4.1 (2.3–32.0) | 0.159 |
| ≥5 ng/mL | 38 (42.2) | 63 (51.2) | 16 (43.2) | 0.385 |
| Stage at diagnosis, n (%) | | | | |
| Localized | 58 (52.7)$_a$ | 63 (47.7)$_a$ | 10 (27.8)$_b$ | |
| Regional invasion | 25 (22.7) | 23 (17.4) | 4 (11.1) | **<0.01** |
| Distant metastasis | 27 (24.5)$_a$ | 46 (34.8)$_a$ | 22 (61.1)$_b$ | |
| Tumour lesions, n (%) | | | | |
| Single lesion | 86 (85.1)$_a$ | 105 (76.6)$_{ab}$ | 23 (62.2)$_b$ | **<0.05** |
| Multiple lesions | 15 (14.9)$_a$ | 32 (23.4)$_{ab}$ | 14 (37.8)$_b$ | |

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG-PS, Eastern Cooperative Oncology Group Performance Status. *Missing values*: ECOG-PS = 6; CA19-9 = 23; CEA = 55; Pattern of growth = 58; Histological grade = 4; Tumour size = 30; Stage at diagnosis = 27. *Statistical analyses*: One-way ANOVA and Kruskal–Wallis tests for continuous variables, and Pearson's Chi-square test for categorical variables were performed by comparing the three Ethnic groups. Different letters in the subscript indicate significant differences between Ethnic groups ($p < 0.05$; a *vs.* b, a *vs.* c, b *vs.* c indicates differences; a and b are not different from ab). Bold indicates significant *p*-values ($p < 0.05$).

***Table 4:*** **Ethnic disparities in clinical and pathological characteristics associated with CCA tumours.**




| | Ethnic group | | |
|---|---|---|---|
| | Caucasian | Hispanic | African |
| **Events**, n (%) | 69 (61.6) | 94 (75.2) | 31 (81.6) |
| **Survival**, median (IQR) | 12.6 (34.0 – 5.4) | 6.0 (15.8 – 1.8) | 8.3 (20.9 – 3.9) |
| **Survival rates**, (%) | | | |
| 6-month | 69.0 | 50.3 | 56.9 |
| 1-year | 51.4 | 31.9 | 29.4 |
| 3-year | 22.1 | 13.8 | 0.0 |
| **HR** (95% CI) | 1 (Ref.) | 1.72 (1.26 – 2.36) | 1.73 (1.09 – 2.75) |
| *p value* | | *<0.001* | *<0.05* |

***Fig. 1:*** **Survival rates of patients with CCA in the LATAM cohort sorted by ethnicity.** Kaplan–Meier analyses and Multivariable Cox regression models were conducted to compare the long-term outcomes among patients with CCA across different ethnic groups. Overall survival was measured from the time of CCA diagnosis until death or the last medical visit. Proportional hazard testing was performed in the Cox regression model to evaluate the effect of the ethnic group on survival while controlling for country of origin. *Abbreviations*: CCA, cholangiocarcinoma; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

Africans (Supplementary Table S2). Among those treated with chemotherapy, the median OS was 7.4 months (IQR: 5.5–13.3) for Caucasians, 9.7 months (IQR: 5.1–14.9) for Hispanics, and 8.3 months (IQR: 5.0–11.5) for Africans (Supplementary Table S2). Although these post-treatment survival results were based on a limited number of patients, they suggest that once treatment is initiated in a timely manner, its effectiveness was similar across ethnic groups.

## Discussion

This study represents the first comprehensive evaluation of the CCA landscape in Latin America. It marks a

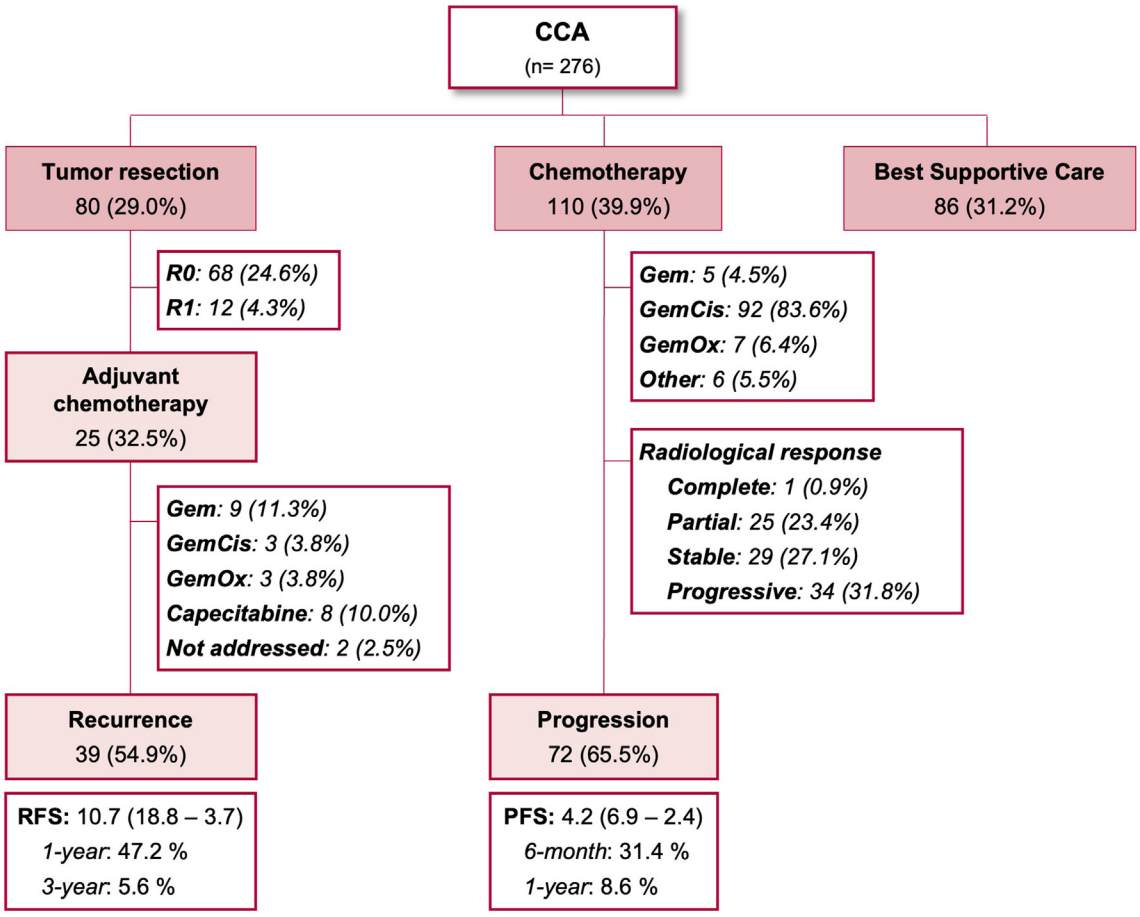
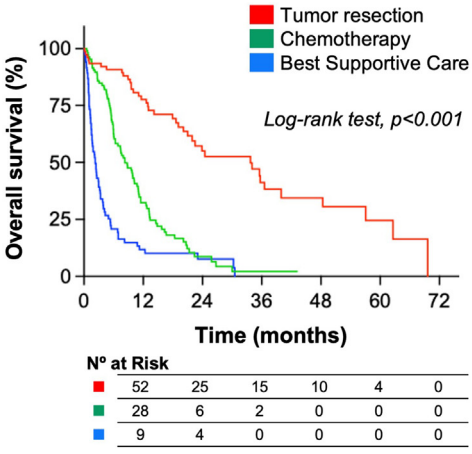



***Fig. 2:* Flowchart describing the therapeutic management and outcomes for patients with CCA in the LATAM cohort.** The chart categorizes patients according to their initial therapeutic strategy: surgery, chemotherapy, or best supportive care. Further information is provided for patients undergoing tumour resection, including details on resection margins and adjuvant chemotherapy. For chemotherapy recipients, details on the type of chemotherapy administered and radiologically assessed response are included. Median relapse- or progression-free survival was calculated using Kaplan–Meier analysis. Only individuals with at least one-year of follow up were included in the analysis, see Supplementary Fig. S1 for more details. Additionally, three patients were treated with locoregional therapies, which, due to their low number, were excluded from the treatment-related analyses. *Abbreviations*: Gem, Gemcitabine; GemCis, Gemcitabine plus cisplatin; GemOx, Gemcitabine plus oxaliplatin; RFS, recurrence-free survival; PFS, progression-free survival.

significant advancement in international collaboration by fostering a multicentre approach that includes institutions with specialized expertise in CCA research and management. The investigation delves deeply into various aspects, encompassing clinical presentation, risk factors, management, outcomes, and the intricate ethnic heterogeneity within the region.

Our data indicate that CCAs in Latin America often originate in the context of a healthy liver, exhibiting a lower prevalence of well-known risk factors such as PSC and inflammatory bowel disease (IBD) than previously reported.[19,20] Geographical variations in PSC prevalence and specific genetic polymorphisms associated with CCA risk in PSC might contribute to the divergent prevalence of PSC observed across CCA cohorts in different regions.[7,21] Conversely, we identified a slightly higher prevalence of cholecystitis and bile duct stones compared to other areas such as Asia and Europe.[22,23] While cholelithiasis is a well-recognized risk factor for gallbladder cancer, emerging evidence also suggests a potential relationship with CCA.[24,25] Bile duct stone disease, affecting only intrahepatic ducts, is rare but can be endemic in specific regions, such as Southeast Asia.[25] In Latin America, Chile and Peru exhibit a high incidence of gallbladder cancer linked with gallstone formation, suggesting an association with lithogenic polymorphisms in specific population groups.[26] However, establishing a direct association with CCA is not straightforward. Chronic liver disease is more commonly linked to HCC, but it also increases the odds for CCA.[27] In this LATAM cohort, we observed a lower rate of cirrhosis or viral hepatitis, at less than 3%,




| | Initial treatment | | |
|---|---|---|---|
| | Tumor resection | Chemotherapy | Best Supportive Care |
| **Events**, n (%) | 40 (50.0) | 85 (77.3) | 72 (83.7) |
| **Survival**, median (IQR) | 33.7 (57.1 – 12.9) | 8.3 (13.4 – 5.2) | 2.3 (5.4 – 1.1) |
| **Survival rates**, (%) | | | |
| 6-month | 89.7 | 64.6 | 20.8 |
| 1-year | 76.7 | 32.4 | 11.9 |
| 3-year | 40.7 | 2.2 | 0.0 |
| **HR** | | 3.59 | 8.20 |
| (95% CI) | 1 (Ref.) | (2.37 – 5-44) | (5.33 – 12.62) |
| *p value* | | *<0.0001* | *<0.0001* |

***Fig. 3:* Survival rates among patients with CCA in the LATAM cohort based on their initial treatment.** Kaplan–Meier analyses and Multivariable Cox regression models were conducted to compare long-term outcomes among patients with CCA following their first therapeutic strategy. Overall survival was measured from the start of initial treatment until death or the last medical visit. *Abbreviations*: IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

compared to other series.[28] This observation may reflect a unique epidemiology or an underrecognized condition.[7,29,30] Metabolic diseases are increasingly recognized as risk factors for CCA.[25] This study suggests that in Latin America, patients with extrahepatic CCA are more frequently overweight or obese compared to those with intrahepatic tumours. This contrasts with previous reports from Europe and North America, where obesity was associated with iCCA, but not extrahepatic CCA.[7,27] A case–control study in China also demonstrated a positive correlation between CCA and metabolic syndrome, associating obesity with both intra- and extrahepatic CCA, while diabetes showed a specific link with iCCA.[31] Although the prevalence of MASLD in our study appeared low, this variable might have been underreported. Given the growing prevalence of metabolic conditions in Latin America, our data underscore the importance of raising awareness and implementing preventive measures in both primary and specialized health services.[32–34]

There was a balanced representation of the three CCA subtypes. Notably, half of the patients with dCCA maintained a preserved performance status at diagnosis, higher than that observed in pCCA and iCCA. iCCA often presented with multiple tumours and a mass-forming pattern, while pCCA and dCCA typically exhibited single lesions with periductal infiltration or intraductal growth, respectively. iCCAs were more often diagnosed with metastatic disease compared to other subtypes. All this aligns with findings from a contemporary European cohort,[7] and reinforce the heterogeneity in CCA subtypes. Moreover, in recent years, it has been acknowledged that molecular features impact the natural course and treatment of CCA. Approximately 50% of iCCAs harbour actionable alterations such as *FGFR* fusions, *IDH1* mutations, *BRAF* mutations, among others. In contrast, dCCA is enriched with non-targetable alterations, such as *TP53* and *CDKN2A*.[2] Thus, further studies should delineate the mutational landscape of CCA tumours in Latin America.

Around 30% of the patients included in our dataset underwent surgery, which is the only potentially curative treatment for CCA. Low rates of resectability were also reported by other groups.[7,35–37] Adjuvant treatment was not widely used in the present cohort, probably due to the lack of solid clinical evidence demonstrating its benefit during the inclusion period.[38] Although patients receiving palliative chemotherapy, mainly based on platinum–gemcitabine combinations,[39,40] demonstrated a survival benefit compared to those receiving best supportive care, the survival curves intersected in the present study. This could be attributed to the heterogeneity among patients in terms of performance status, differing responses to chemotherapeutic agents, and risk factors, among others. Such intersections are common even in controlled clinical trials,[41] highlighting the complex interplay between patients' individual characteristics and treatment efficacy. Locoregional therapies were not significantly adopted in this cohort, although some studies have explored their potential role in patients with locally advanced tumours, including transarterial embolization, radiotherapy, or intra-arterial chemotherapy.[42] Further studies are warranted to evaluate specific subgroups that may benefit from locoregional therapy alone or in combination with systemic treatment.

Historically, Latin America exhibits a rich diversity in ancestry, culture, and ethnicity, influenced by native Americans, Africans, and Europeans.[43] However, this history of conquest and intermixing has led to stratified

societies, both ethnically and economically. Despite potential biases from retrospective data, our study reveals disparities in the prevalence of risk factors, cancer presentation, and OS within Latin American populations. Specifically, we observed varying occurrences of CCA subtypes, with iCCAs being more common in Hispanic and African populations, and dCCA being more prevalent among Caucasians, warranting further validation. Importantly, survival outcomes were better in Caucasians compared to Africans and Hispanics. This highlights systemic barriers to cancer screening, unravelling disparities in healthcare access among individuals from diverse ethnic backgrounds and potentially lower socioeconomic status. The healthcare system in Latin America is predominantly funded publicly, with less than 30% of the population having access to private healthcare. The participating centres rely on universal healthcare systems and have access to CCA treatments recommended by standard practices. However, socioeconomic conditions can still impact health outcomes. Our study indicates that, while clinical management is broadly equitable, African ethnicity is associated with later diagnosis, a higher frequency of metastatic disease, poorer ECOG performance status, and lower BMI, potentially contributing to worse outcomes for this group. However, when stratified by therapeutic strategy, post-treatment outcomes were similar across ethnic groups. This suggests that timely detection and treatment could help mitigate disparities among ethnic subgroups.

This context is implicit in this cohort, suggesting that the interrelationships between sociocultural factors, economic disparity, and ethnicity can directly influence the results. The duration between the first reported symptom and referral to a tertiary cancer centre would likely explain the differential distribution of stage and performance status and, eventually, outcomes. In Brazil, for example, there is a prevalence of Caucasians in the capitals of the Southeast, where most of the large-volume cancer centres are geographically located. On the other hand, there is a clear wealth imbalance that disadvantages African and Hispanic descendants, potentially affecting education, symptom recognition, access to healthcare services, and geographic proximity to cancer centres, thereby reducing opportunities for receiving active oncological treatments. Notably, a large proportion of Hispanics in our study did not receive any anti-cancer therapy. This scenario underscores the need for educational programs aimed at increasing patients' awareness of the availability of beneficial treatments and symptom recognition.[44,45] Ultimately, this impacts eligibility for curative-intent surgery and the consequent survivorship outcomes.[46] Alarmingly, Latin Americans are underrepresented in clinical trials for biliary malignancies, and genomic research predominantly involves individuals of European ancestry, necessitating more inclusive studies. Addressing these disparities requires multifaceted approaches, including culturally sensitive screening programs, enhanced education, and equitable resource distribution. By acknowledging and rectifying these disparities, healthcare systems can work towards alleviating the cancer burden in Latin American communities and improving health outcomes for individuals affected by CCA and other cancers.

### Limitations

The present study has several limitations that need to be acknowledged, and the results must be interpreted cautiously. It relies on data obtained from a limited number of reference centres, preventing it from being considered an epidemiological or comprehensive demographic study. Additionally, underreporting and underdiagnosis of CCA cases, particularly from remote areas of Latin America, may introduce bias into the results of the present study. Moreover, selection bias may influence the distribution of patients across disease stages, depending on the specialty focus of each local research group (e.g., surgeons, hepatologists, medical oncologists). Furthermore, the retrospective nature of the study, coupled with its status as an investigator-reported cohort study, may introduce potential biases in reporting tumour stage and location, baseline characteristics, comorbidities, and variations in management approaches across different centres. It is worth noting that while no external audit was conducted, each centre performed an internal review to validate the accuracy of the included data. Nevertheless, the absence of a central review should not significantly impact the conclusions drawn from this study, as the data were curated by investigators affiliated with referral hospitals possessing extensive experience in managing CCA. Self-reporting of ethnicity by individuals, while commonly employed, presents a limitation as it relies on subjective classification. Self-identified ethnic groups may display genetic admixture, with some African Americans having predominantly European ancestry, and *vice versa*. This variability extends to Hispanic populations, where self-reported ancestry may not accurately reflect individual genomic characteristics, thereby impacting outcome predictability. Further studies are warranted to investigate the role of ethnicity within different countries and continents, considering socio-economic, genetic, environmental factors, and regional healthcare structures.

In conclusion (Fig. 4), our study provides the first multicentric analysis of baseline characteristics and therapeutic management of CCA in Latin America. The role of metabolic diseases in CCA epidemiology appears to be relevant and warrants attention from medical societies and the population. The diagnosis of CCA at advanced stage is a major concern and has a clear impact on prognosis. Implementing surveillance strategies for patients with risk factors could help address this issue. Differences among ethnicities reveal that Africans are diagnosed with CCA at more advanced

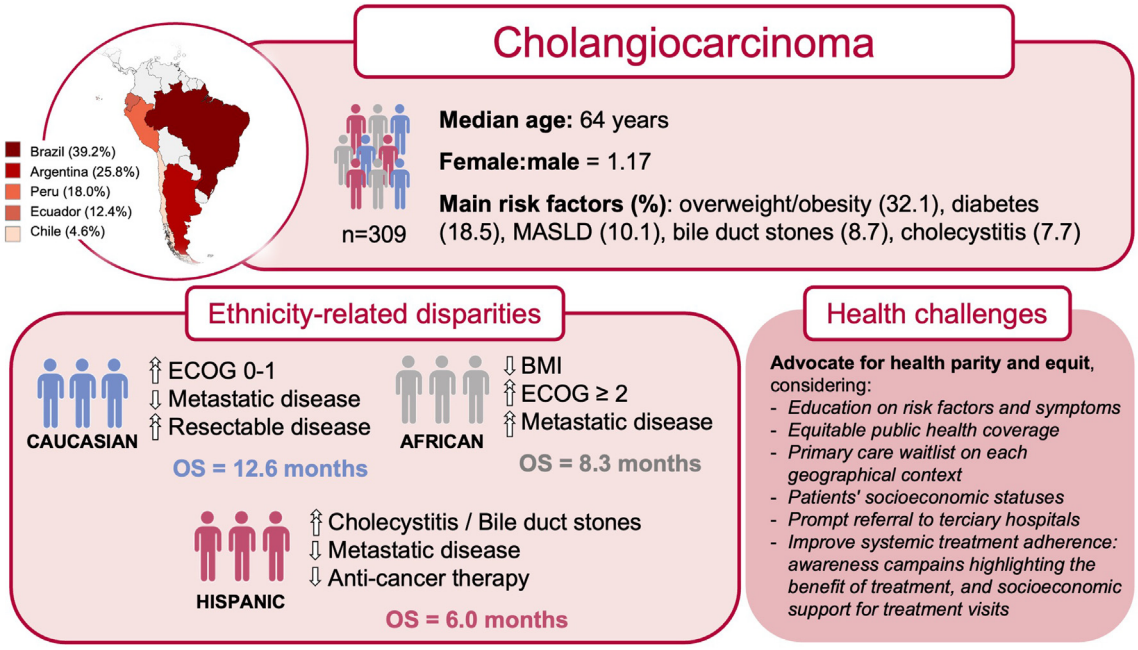



*Fig. 4:* **Graphical abstract**.

stages, and Hispanics are less frequently treated with chemotherapy for disseminated disease. As a result, Caucasians have better survival rates compared to both Hispanics and Africans. Therefore, there is a need to increase awareness and education about CCA among both the general population and healthcare providers, as well as to implement measures to mitigate structural inequalities in healthcare in Latin America.

#### Contributors

*LGF*: study concept and design, analysis and interpretation of data, statistical analysis, and drafting of the manuscript. *LI-S*: study concept and design, raw data preprocessing, verification of data and statistical analysis, result interpretation, and drafting of the manuscript. *PHH, YC, ELB, CZ, SAS, AB, FJC, MA, JCR, EC, JDF, DB*, and *CPO*: data acquisition and proof-reading. *AB, JDD*, and *LB*: funding and proof-reading. *PMR*: analysis and interpretation, drafting of the manuscript, and proof-reading. *IR*: study design, assistance on ethical issues, and proof-reading. *JMB*: study concept and design, analysis and interpretation of data, statistical analysis, drafting of the manuscript, funding, and final responsibility for the decision to submit the manuscript for publication.

#### Data sharing statement

The data generated and analysed in this cohort study are not publicly available due to participant privacy and confidentiality agreements. De-identified data may be made available to qualified researchers upon reasonable request for the purpose of replicating results, subject to approval by the appropriate ethics committees. Data access requests should be directed to the corresponding author, Prof. Jesus M. Banales.

#### Declaration of interests

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100952.

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