Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Tumor factors, but not cirrhosis, drive the development of baseline and incident ascites in surgically resected cholangiocarcinoma: a retrospective cohort study

Yeou-Yu Teng
Taipei Veterans General Hospital
Yu-Jen Chen
yzchen5@vghtpe.gov.tw

Taipei Veterans General Hospital
Chun-Ting Ho
Taipei Veterans General Hospital
Pei-Chang Lee
Taipei Veterans General Hospital
Tsung-Chieh Yang
Taipei Veterans General Hospital
Hui-Chun Huang
Taipei Veterans General Hospital
Yi-Hsiang Huang
Taipei Veterans General Hospital
Ming-Huan Chen
Taipei Veterans General Hospital
Nai-Jung Chiang
Taipei Veterans General Hospital
Jiing-Chyuan Luo
Taipei Veterans General Hospital
Ming-Chih Hou
Taipei Veterans General Hospital
Jaw-Ching Wu
Taipei Veterans General Hospital
Chien-Wei Su
Taipei Veterans General Hospital

Research Article

Keywords: cholangiocarcinoma, ascites, risk factors, portal hypertension, overall survival

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11228927/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Portal hypertension-related complications have emerged as important prognostic determinants in patients with cholangiocarcinoma (CCA), yet the clinical impact and pathophysiological drivers of ascites in this population have never been systematically investigated. This study aimed to clarify the impact of ascites on overall survival (OS) in patients with surgically resected CCA using a time-dependent approach and to identify the risk factors underlying baseline and incident ascites.

Methods

We retrospectively reviewed patients with CCA who underwent surgical resection at Taipei Veterans General Hospital between January 2013 and December 2023. Of 842 patients screened, 195 with an available histological ISHAK fibrosis assessment formed the cirrhosis-assessed cohort (baseline ascites, n = 55; no baseline ascites, n = 140). Ascites was modeled as a time-dependent covariate in a Cox analysis of OS to avoid immortal-time bias; risk factors for baseline ascites (logistic regression) and incident ascites (cause-specific Cox regression) were examined, with multiple imputation for missing data.

Results

Patients with baseline ascites had more late-stage tumors (III–IV, 40.0% vs. 21.6%, p = 0.009), higher CA19-9 (p = 0.001), and worse ALBI scores (p = 0.045), whereas the prevalence of cirrhosis (ISHAK > 4) did not differ (27.3% vs. 22.9%, p = 0.517). Baseline ascites was associated with worse OS (median 876 vs. 2026 days, log-rank p = 0.037). In the adjusted time-dependent model, baseline ascites (HR 1.94, 95% CI 1.12–3.38, p = 0.018) and incident ascites (HR 3.24, 95% CI 1.81–5.80, p < 0.001) independently predicted OS; ALBI grade 2/3 (HR 2.14, p = 0.002) and CA19-9 > 38 U/mL (HR 2.03, p = 0.003) were also independent predictors. Baseline ascites was independently driven by tumor factors (CA19-9 > 38 U/mL: OR 2.22, p = 0.027; clinical stage per stage: OR 1.40, p = 0.049), whereas incident ascites was driven by clinical stage (HR 1.60, p = 0.007) and macrovascular invasion (HR 4.56, p = 0.002).

Conclusions

In surgically resected CCA patients, baseline and incident ascites were driven predominantly by tumor factors—not by the structural status of cirrhosis—and both, particularly incident ascites, were in turn independently associated with poorer survival. Tumor factors, but not cirrhosis, determined the development of ascites in this population.

Background

Cholangiocarcinoma (CCA) is the second most common primary liver malignancy, which carries an unfavorable prognosis, and its incidence and mortality are rising worldwide [1, 2]. In Taiwan, the age-standardized incidence of intrahepatic CCA rose from 1.51 to 4.07 per 100,000 between 1993–1997 and 2013–2017, accompanied by a shift toward younger patients [3]. Despite advances in surgical resection and the establishment of gemcitabine–cisplatin as the standard systemic therapy for advanced disease [4], most patients still present at an advanced stage, and their long-term survival remains poor even after curative-intent surgical resection [1]. Identifying prognostically informative clinical markers therefore remains a priority in the management of these patients.

Beyond the tumor itself, complications of portal hypertension are also increasingly recognized as important prognostic factors in patients with hepatobiliary malignancy. According to the Baveno VII consensus, the transition from compensated to decompensated liver disease, which is signaled by ascites, variceal hemorrhage, or hepatic encephalopathy, marks a major deterioration in prognosis [5]. CCA is of particular interest here, since it frequently coexists with biliary obstruction, direct hepatic parenchymal invasion, and underlying chronic liver disease, and all of these may promote portal hypertension and the formation of ascites [1, 2]. Our team previously showed that esophagogastric varices (EGV) are an independent risk factor for poorer OS in patients with CCA. In that study of 923 patients with CCA, of whom 321 underwent esophagogastroduodenoscopy, the prevalence of EGV was 14.6%, and the presence of EGV independently predicted worse OS (HR 1.823, 95% CI 1.248–2.663, p = 0.002); a FIB-4 index > 2.67 and an ALBI grade > 1 were predictive of EGV [6]. The present study comes from the same institutional CCA database, and it focuses on the surgically resected subgroup in which hepatic fibrosis could be histologically assessed. In a related work from the same cohort, we further found that a simple composite of the Fibrosis-4 index and imaging-defined ascites, the FAB classification, added prognostic value beyond cancer stage in patients with CCA [7].

Ascites is one of the most clinically evident manifestations of portal hypertension and hepatic decompensation, and its development often signals a transition to a more advanced disease state [5]. In cirrhosis and hepatocellular carcinoma (HCC), ascites classically results from sinusoidal portal hypertension caused by structural fibrosis [5]. In CCA, however, ascites could arise not only from underlying chronic liver disease but also from tumor-related mechanisms, such as peritoneal spread, malignant obstruction, and exudation. Nevertheless, the clinical role, prognostic weight, and determinants of ascites in patients with CCA have never been systematically investigated. In particular, it remains unknown whether ascites in CCA reflects underlying structural cirrhosis, tumor-driven physiology, or declining hepatic functional reserve, and whether ascites present at baseline differs from ascites that develops during follow-up in its determinants and prognostic meaning.

Therefore, building on our team's ongoing work on portal hypertension-related complications in CCA, this study aimed to (a) clarify how ascites affects OS in surgically resected patients with CCA, using a time-dependent analysis that distinguishes baseline from incident ascites while avoiding immortal-time bias,

and (b) identify the risk factors behind both baseline and incident ascites, thereby advancing our understanding of the pathophysiological mechanisms of ascites formation in this population.

Methods

Patients and follow-up

We retrospectively reviewed patients with a diagnosis of CCA at Taipei Veterans General Hospital between January 2013 and December 2023. To enable histological grading of hepatic fibrosis, this study was restricted to patients who underwent surgical resection, in whom the ISHAK fibrosis score could be evaluated on the resected specimen. As shown in the study flow diagram (Figure 1), 842 patients with CCA were screened, and 195 patients with an available ISHAK fibrosis assessment constituted the final cirrhosis-assessed cohort. Patients were classified according to the presence of ascites at baseline into a baseline ascites group (n = 55) and a no baseline ascites group (n = 140). For the analysis of incident ascites, patients without baseline ascites and with a positive time at risk (incident ascites-free survival > 0 days) formed the at-risk population (n = 138), among whom 57 incident ascites events were observed.

Follow-up was calculated from the date of the initial CCA diagnosis to the date of death; surviving patients were censored at the date of the last follow-up or at the end of the study (January 31, 2024).

Definitions

Ascites. Ascites was defined as the presence of free intraperitoneal fluid detected by imaging, namely ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI). The clinical framing of ascites as a hallmark of hepatic decompensation followed the Baveno VII consensus [5]. Baseline ascites was defined as ascites present at or before the time of the index diagnosis/resection, coded as present from day 0. Incident ascites was defined as new-onset ascites developing during follow-up in a patient without baseline ascites, with the event date set at the date of ascites onset.

Cirrhosis and fibrosis. Structural cirrhosis was defined histologically as an ISHAK fibrosis score > 4 on the resected specimen [8]. The FIB-4 index was calculated and dichotomized at > 2.67 [9].

Clinical staging. Tumors were staged according to the American Joint Committee on Cancer (AJCC) staging system, using the 7th or 8th edition corresponding to the edition in use at the time of diagnosis [10, 11]. In the risk-factor models (Tables 3 and 4), clinical stage was entered as an ordinal continuous variable (stages I–IV coded 1–4, with the OR/HR representing the incremental risk per one-stage increase); in the baseline comparison (Table 1), stage was dichotomized as late stage (III–IV).

Laboratory markers and cutoffs. Hepatic functional reserve was assessed by the ALBI grade (grade 2/3 vs. grade 1) [12]. CA19-9 was dichotomized at > 38 U/mL and ALP at > 100 U/L, per routine clinical convention.

Outcomes and competing risks. OS was defined as the interval from the initial CCA diagnosis to death from any cause. This study focused specifically on ascites rather than on hepatic decompensation in general. Accordingly, for the incident-ascites analysis the outcome was incident ascites-free survival, defined as the time from diagnosis to the development of incident ascites (imaging-detected new-onset ascites during follow-up); death and the other forms of first hepatic decompensation (hepatic encephalopathy or variceal bleeding) were treated as competing events in a cause-specific framework, and patients who remained ascites-free were censored at the last follow-up. A patient whose first decompensation event was variceal (EV) bleeding (n = 1) was reclassified as a non-event (censored) rather than counted as an ascites or competing event; because that patient's ascites-event indicator was already 0, this reclassification did not alter the reported hazard ratios.

Statistical analysis

Continuous variables were expressed as the median (interquartile range, IQR) and compared using the Mann–Whitney U test. Categorical variables were expressed as n (%) and compared using the chi-square test or Fisher's exact test as appropriate. OS was estimated using the Kaplan–Meier method and compared with the log-rank test.

To avoid immortal-time bias arising from the time-varying nature of incident ascites [13], ascites was modeled as a time-dependent covariate in a Cox proportional hazards model of OS: patients with baseline ascites were coded as exposed (=1) from day 0; patients with incident ascites transitioned from unexposed to exposed (=1) at the date of ascites onset; and patients who never developed ascites remained unexposed (=0) throughout. Risk factors for baseline ascites were analyzed by logistic regression, and risk factors for incident ascites by cause-specific Cox regression within a competing-risks framework, because the Kaplan–Meier method overestimates cumulative incidence when competing events such as death are present [14]. For all multivariable models, variables with statistical significance ($P < 0.05$) or near significance ($P < 0.10$) in the univariate analysis were entered into the multivariate model. Binary variables were recoded as 0 = reference / 1 = risk factor present.

Missing data were addressed by multiple imputation using multivariate imputation by chained equations (MICE, statsmodels) with m = 20 imputed datasets, combined by Rubin's rules on the log scale [15]. Continuous source variables (CA19-9, ALP) were imputed on the continuous scale and the binary cutoffs (> 38 / > 100) were then derived (100% concordant with the original coding). For the survival models (Tables 2 and 4), the imputation models included the event indicator and the Nelson–Aalen cumulative hazard, following the recommendations of White and Royston [16]. Univariate screening was performed on complete cases; multivariable models were then re-estimated on the full sample to eliminate listwise deletion. Complete-case analyses are presented as sensitivity analyses. Robustness to the timing of surgery was further examined in sensitivity analyses that adjusted the time-dependent survival model for the diagnosis-to-resection interval and that re-anchored the survival time origin at the date of resection.

A two-tailed P value of less than 0.05 was considered statistically significant. All analyses were performed using Python 3 (pandas, statsmodels, and lifelines).

The study was executed in accordance with the Declaration of Helsinki and had been approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan (IRB No. 2024-08-004AC). As this was a retrospective, observational cohort study, the requirement for informed consent was waived. Patient information was anonymized and de-identified before analysis.

Results

Baseline characteristics

The baseline characteristics of the 195 patients stratified by the presence of baseline ascites are summarized in Table 1. Patients with baseline ascites had a significantly higher proportion of late-stage (III–IV) tumors (40.0% vs. 21.6%, p = 0.009) and higher serum CA19-9 (median 63.7 vs. 22.3 U/mL, p = 0.001), reflecting greater tumor burden and activity. They also had a marginally worse ALBI score (−2.7 vs. −2.8, p = 0.045); this small difference did not persist when the ALBI grade was dichotomized for the risk-factor models, consistent with a limited clinical contribution of hepatic reserve to baseline ascites. Of note, the prevalence of structural cirrhosis (ISHAK > 4) did not differ between the two groups (27.3% vs. 22.9%, p = 0.517), nor did FIB-4 > 2.67 (34.5% vs. 30.9%, p = 0.623). The remaining demographic, virological, and biochemical variables were comparable between groups (Table 1). Esophagogastric varices were not tabulated, as endoscopic assessment was not performed in all patients. These findings suggest that ascites in this population is associated primarily with tumor activity and, to a lesser extent, with hepatic functional reserve, rather than with structural fibrosis per se.

Impact of ascites on overall survival

During a median follow-up of 1190 days (reverse Kaplan–Meier estimate), 88 of the 195 patients died. Kaplan–Meier analysis showed that patients with baseline ascites had significantly worse OS than those without (median OS 876 vs. 2026 days; 1-year 74% vs. 85%; 3-year 39% vs. 60%; log-rank p = 0.037; Figure 2). Because baseline ascites is defined at day 0, this comparison is not subject to immortal-time bias.

To incorporate incident ascites correctly and to distinguish it from baseline ascites, we modeled ascites as a time-dependent covariate (Table 2). When any ascites was treated as a single time-dependent covariate, the presence of ascites was strongly associated with mortality (HR 3.59, 95% CI 2.27–5.70, p < 0.001; Model A). When baseline and incident ascites were separated (reference = no ascites), incident ascites carried a higher risk than baseline ascites (incident HR 5.21, 95% CI 3.06–8.90, p < 0.001 vs. baseline HR 2.78, 95% CI 1.65–4.69, p < 0.001; Model B). In the adjusted, multiply imputed model on the full sample (Model C, n = 195), both baseline ascites (HR 1.94, 95% CI 1.12–3.38, p = 0.018) and incident ascites (HR 3.24, 95% CI 1.81–5.80, p < 0.001) remained independent predictors of OS, with incident

ascites again carrying the higher risk. ALBI grade 2/3 (HR 2.14, 95% CI 1.33–3.44, p = 0.002) and CA19-9 > 38 U/mL (HR 2.03, 95% CI 1.26–3.27, p = 0.003) were also independent predictors, whereas age ≥ 65 and clinical stage were not (Table 2). Notably, after removal of immortal-time bias [13], the mortality risk associated with incident ascites exceeded that of baseline ascites (Table 2).

Risk factors for baseline ascites

Risk factors for the presence of baseline ascites were examined by logistic regression (Table 3). On univariate analysis, CA19-9 > 38 U/mL (OR 2.84, 95% CI 1.47–5.50, p = 0.002) and clinical stage (per stage, OR 1.59, 95% CI 1.16–2.19, p = 0.004) were significantly associated with baseline ascites. On multivariable analysis using the full sample with multiple imputation, both remained independent risk factors (CA19-9 > 38 U/mL: OR 2.22, 95% CI 1.10–4.49, p = 0.027; clinical stage per stage: OR 1.40, 95% CI 1.00–1.96, p = 0.049). In contrast, structural cirrhosis (ISHAK > 4), ALBI grade, tumor location (eCCA vs. iCCA), and age were not significantly associated with baseline ascites (Table 3). The complete-case multivariable analysis (n = 178) yielded concordant results (CA19-9 > 38 U/mL: OR 2.21, p = 0.027; clinical stage: OR 1.44, p = 0.038). These findings indicate that baseline ascites is predominantly driven by tumor factors.

Risk factors for incident ascites

Risk factors for incident ascites were examined by cause-specific Cox regression in the at-risk population without baseline ascites (n = 138, 57 events), with death and other first decompensation events treated as competing risks (Table 4). Because this analysis was the most sensitive to missing data, the multiple-imputation results on the full sample (n = 138) are presented as the primary analysis, and the complete-case analysis (n = 113) as a sensitivity analysis.

In the primary multiply imputed model, clinical stage (per stage, HR 1.60, 95% CI 1.14–2.26, p = 0.007) and macrovascular invasion (HR 4.56, 95% CI 1.75–11.90, p = 0.002) were independent risk factors for incident ascites, whereas ALP > 100 U/L (HR 1.98, 95% CI 0.99–3.97, p = 0.054) and ALBI grade 2/3 (HR 1.65, 95% CI 0.92–2.96, p = 0.096) were of borderline significance. In the complete-case sensitivity analysis (n = 113), the independently significant factors were clinical stage (HR 1.57, p = 0.018), macrovascular invasion (HR 3.66, p = 0.014), and ALBI grade 2/3 (HR 2.63, p = 0.006), whereas ALP > 100 U/L was not significant (p = 0.278). Clinical stage and macrovascular invasion were robustly significant in both analyses; ALBI grade, significant in the complete-case model, attenuated to borderline after imputation of the 25 additional patients excluded by listwise deletion, whereas ALP approached significance. This sensitivity to missing-data handling suggests that part of the complete-case ALBI effect reflected selective exclusion, and the imputed results should be regarded as more reliable. Structural cirrhosis (ISHAK > 4) was not an independent risk factor for incident ascites in either analysis (Table 4). Taken together, incident ascites was driven principally by tumor stage and macrovascular invasion, with hepatic reserve (ALP and ALBI) contributing at a borderline level.

Sensitivity analyses

The median interval from the initial diagnosis to surgical resection was 26 days (IQR 12–46). In the time-dependent survival model, adding the diagnosis-to-surgery interval as a covariate left the ascites associations essentially unchanged (baseline ascites HR 2.05, 95% CI 1.12–3.75; incident ascites HR 3.25, 95% CI 1.71–6.17), and the interval itself was not associated with OS (HR 1.00, p = 0.93). Re-anchoring the survival time origin at the date of resection yielded a concordant direction, with worse OS among patients with baseline ascites (median 857 vs. 1998 days; log-rank p = 0.077). The complete-case multivariable analyses (Tables 3 and 4) were likewise concordant with the multiply imputed results for the principal risk factors. Together, these analyses indicate that the findings were robust to the handling of missing data and to the definition of the survival time origin.

Discussion

This study has several major findings. First, in surgically resected patients with CCA, ascites independently affected OS after properly handling immortal-time bias, and incident ascites carried a higher mortality risk than baseline ascites. Second, baseline ascites was driven mainly by tumor factors, namely higher CA19-9 and more advanced clinical stage. Third, incident ascites was driven mainly by advanced clinical stage and macrovascular invasion, with hepatic functional reserve (ALP and ALBI) contributing at a borderline level. Finally, cirrhosis (ISHAK > 4) neither differed between the ascites groups nor independently predicted either baseline or incident ascites, suggesting that ascites here is not simply a marker of structural fibrosis.

The independent prognostic impact of ascites extends our team's work on portal hypertension-related complications in CCA. As we previously reported, EGV independently predicted poorer OS in CCA, and FIB-4 and ALBI predicted varices [6]. The present findings fit this pattern: ascites and ALBI grade carried prognostic weight, whereas the mere histological presence of cirrhosis did not. This agrees with prior CCA-specific evidence that ALBI grade stratifies survival in intrahepatic CCA [17], pointing to the contribution of hepatic functional reserve rather than structural fibrosis. Together, these results reveal a consistent theme: portal hypertension-related indices carry prognostic significance in CCA, whereas the structural status of cirrhosis does not.

The distinct risk-factor profiles of baseline and incident ascites offer insight into how ascites forms in CCA, which may differ fundamentally from the classic mechanism in cirrhosis and HCC, where ascites is predominantly attributed to sinusoidal portal hypertension from structural fibrosis [5]. In our surgical cohort, by contrast, baseline ascites was driven by tumor factors alone (CA19-9 and stage) rather than by cirrhosis or hepatic reserve, suggesting that ascites present at diagnosis largely reflects tumor activity. Possible mechanisms, such as occult peritoneal dissemination or carcinomatosis, malignant lymphatic or portal obstruction, and tumor-related exudation, are recognized causes of malignant ascites in intra-abdominal cancers [18], and could generate ascites without advanced structural fibrosis. These mechanisms, however, could not be directly measured here.

Incident ascites, by contrast, reflected tumor stage and macrovascular invasion, with hepatic reserve (ALP and ALBI) contributing at a borderline level. Tumor progression and macrovascular invasion may compromise portal venous inflow and trigger localized or segmental portal hypertension, while a concurrently declining hepatic reserve may lower the threshold at which fluid homeostasis fails, together leading to new-onset ascites—a convergence of tumor-driven vascular compromise and functional decompensation rather than the slowly progressive structural portal hypertension seen in cirrhosis. Our findings thus both align with and diverge from previous research. Ascites retained its prognostic importance, as in cirrhosis and advanced HCC where it independently predicts poorer survival [19], yet across both forms its determinants here were tumor-related and functional rather than structural. This supports the central theme of our study: tumor factors, but not the status of cirrhosis, drove the development of ascites.

A further explanation may lie in the timing relationship between each marker and the resection. CA19-9, associated with baseline but not incident ascites, primarily reflects the original tumor burden at diagnosis and is a well-established preoperative prognostic marker in resectable CCA, where an elevated level predicts worse survival and correlates with locally advanced or metastatic disease [20, 21]. Because baseline ascites and the primary tumor coexist preoperatively, an elevated CA19-9 would be expected to track with baseline ascites. However, curative-intent resection largely removes the primary tumor burden that CA19-9 represents, which may explain its lesser relevance to ascites developing after surgery, although we did not analyze postoperative CA19-9 kinetics. Clinical stage and macrovascular invasion, by contrast, are recognized high-risk features for recurrence after resection [22, 23], and most patients eventually recur even after complete resection [24], with a median recurrence-free survival of roughly two years or less in resected biliary tract cancer [25]. That incident ascites was driven by these recurrence-associated features suggests it may be closely linked to tumor recurrence rather than residual primary burden. Thus, baseline ascites may reflect the tumor burden present at diagnosis, and incident ascites its recurrence. Notably, neither was associated with structural cirrhosis (ISHAK score).

The higher risk carried by incident than baseline ascites deserves attention. Analyzed by a simple Kaplan–Meier approach anchored at diagnosis, the risk of new-onset ascites is systematically underestimated, because a patient must survive long enough to develop it before being counted as exposed—the hallmark of immortal-time bias [13]. The time-dependent model removed this bias, and incident ascites emerged as a strong marker of impending death, perhaps signaling acute deterioration in the balance between tumor burden and hepatic reserve. This interpretation should remain cautious, as ascites, tumor activity, and hepatic reserve are closely linked to one another, and causality cannot be established from observational data.

Several limitations should be noted. First, this is a single-center retrospective study, so the findings are subject to selection bias and unmeasured confounding; nonetheless, the cohort was drawn from a well-characterized institutional CCA database with detailed clinical and histological annotation. Second, ascites was defined radiologically, and we lacked ascitic fluid analysis. The serum-ascites albumin gradient (SAAG) classifies ascites as portal hypertension-related (SAAG ≥ 1.1 g/dL) or non-portal-

hypertensive [26], but it does not identify a malignant cause, since malignant ascites in CCA, particularly with extensive hepatic involvement or tumor-related portal or hepatic venous obstruction, frequently also shows a high SAAG [18]. Ascitic cytology is sensitive mainly when the mechanism is peritoneal carcinomatosis, and it is typically negative when tumors cause ascites through other routes such as hepatic metastatic infiltration or portal obstruction, so a negative cytology does not exclude a tumor-related etiology [27]. We therefore cannot cleanly separate the tumor-related and portal hypertension-related contributions to ascites, even with fluid analysis. Still, the risk-factor findings—predominant tumor factors and no independent cirrhosis effect—point toward a mainly tumor-driven mechanism. Third, surveillance bias is possible: patients under closer follow-up may have had incident ascites detected more readily or earlier, which could bias its estimated incidence and timing. The direction of this bias is unclear; that said, clinically meaningful ascites eventually becomes symptomatic, and imaging surveillance of CCA at our institution is relatively standardized. Fourth, restricting the analysis to surgically resected patients, necessary for histological fibrosis grading, introduces selection toward operable disease and prevents extrapolation to unresectable CCA. Given the diagnosis-to-resection interval, this also raises potential immortal-time bias [13]. Nevertheless, histological assessment of cirrhosis is a strength rarely available in CCA cohorts, and sensitivity analyses adjusting for the diagnosis-to-surgery interval and re-anchoring the time origin at resection, described in the "Sensitivity analyses" section of the Results, supported the robustness of our findings. Fifth, the sample size and event numbers were limited, and the incident-ascites model in particular came close to the recommended threshold for events per variable, which carries some risk of overfitting; however, the multiply imputed and complete-case analyses agreed on the main findings. Sixth, several variables had missing values, handled with multiple imputation [15]; the ALBI and ALP effects for incident ascites were sensitive to how missing data were handled and should be interpreted with caution. Finally, causality cannot be established from a retrospective design, and some potentially relevant factors, including direct hemodynamic measures of portal hypertension such as the hepatic venous pressure gradient, could not be included.

Conclusions

In surgically resected patients with CCA, both baseline and incident ascites were driven mainly by tumor factors—tumor activity (CA19-9 and stage) for baseline ascites and recurrence-associated features (stage and macrovascular invasion) for incident ascites—rather than by the structural status of cirrhosis, which was associated with neither. Both forms of ascites, especially incident ascites, were in turn independently associated with poorer OS. Tumor factors, but not the status of cirrhosis, determined the development of ascites. Further prospective studies with larger cohorts are needed to confirm these findings and to clarify how ascites forms in CCA and whether it can serve as a prognostic and therapeutic target.

Abbreviations

AJCC: American Joint Committee on Cancer; ALBI: albumin–bilirubin; ALP: alkaline phosphatase; CA19-9: carbohydrate antigen 19-9; CCA: cholangiocarcinoma; CI: confidence interval; CT: computed tomography; EGV: esophagogastric varices; EV: esophageal varices; FIB-4: Fibrosis-4 index; HCC: hepatocellular carcinoma; HR: hazard ratio; IQR: interquartile range; IRB: Institutional Review Board; MICE: multivariate imputation by chained equations; MRI: magnetic resonance imaging; OR: odds ratio; OS: overall survival; SAAG: serum-ascites albumin gradient.

Declarations

Ethics approval and consent to participate

The study was executed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan (IRB No. 2024-08-004AC). Owing to the retrospective, observational design, the Institutional Review Board waived the requirement for informed consent. Patient information was anonymized and de-identified before analysis.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available because they contain information that could compromise patient privacy, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Y.L. Lin Hung Tai Education Foundation and the Szu-Yuan Research Foundation of Internal Medicine. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Authors' contributions

YYT drafted the manuscript and prepared the tables and figures. YJC conceived and designed the study, performed the statistical analyses, supervised the work, and is the guarantor of the article. CTH, PCL, TCY, HCH, YHH, MHC, NJC, JCL, and MCH contributed to patient care, data acquisition, and interpretation of the data. JCW and CWS critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Banales JM, Marin JJG, Lamarca A, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17(9):557–88. 10.1038/s41575-020-0310-z.
2. Brindley PJ, Bachini M, Ilyas SI, et al. Cholangiocarcinoma Nat Rev Dis Primers. 2021;7(1):65. 10.1038/s41572-021-00300-2.
3. Lin CR, Lee YK, Chiang CJ, et al. Secular trends of intrahepatic cholangiocarcinoma in a high endemic area: a population-based study. World J Gastroenterol. 2022;28(28):3695–705. 10.3748/wjg.v28.i28.3695.
4. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81. 10.1056/NEJMoa0908721.
5. de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII—Renewing consensus in portal hypertension. J Hepatol. 2022;76(4):959–74. 10.1016/j.jhep.2021.12.022.
6. Ma TH, Chen YJ, Ho CT, Lee PC, Yang TC, Huang HC, Huang YH, Chen MH, Luo JC, Hou MC, Wu JC, Su CW. The Impact of Esophagogastric Varices on the Outcomes of Patients With Cholangiocarcinoma. Clin Transl Gastroenterol. 2025;16(12):e00930. 10.14309/ctg.0000000000000930.
7. Chen YF, Chen YJ, Ho CT, Lee PC, Yang TC, Huang HC, Huang YH, Chen MH, Luo JC, Hou MC, Wu JC, Su CW. A simple composite of ascites and Fibrosis-4 index adds prognostic value beyond cancer stage in cholangiocarcinoma: a retrospective cohort study. Ann Hepatol. Submitted; manuscript no. ANNHEPATOL-S-26-00757.
8. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22(6):696–9. 10.1016/0168-8278(95)80226-6.
9. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25. 10.1002/hep.21178.

10. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
11. Amin MB, Edge SB, Greene FL, et al. editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
12. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol. 2015;33(6):550–8. 10.1200/JCO.2014.57.9151.
13. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167(4):492–9. 10.1093/aje/kwm324.
14. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601–9. 10.1161/CIRCULATIONAHA.115.017719.
15. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: Wiley; 1987.
16. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med. 2009;28(15):1982–98. 10.1002/sim.3618.
17. Kaneko S, Kurosaki M, Tsuchiya K, et al. Prognosis of intrahepatic cholangiocarcinoma stratified by albumin-bilirubin grade. Hepatol Res. 2021;51(8):902–8. 10.1111/hepr.13673.
18. Bleicher J, Lambert LA. A palliative approach to management of peritoneal carcinomatosis and malignant ascites. Surg Oncol Clin N Am. 2021;30(3):475–90. 10.1016/j.soc.2021.02.004.
19. Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology. 2015;61(1):184–90. 10.1002/hep.27443.
20. Wang Z, Shi Y, Xiong G, Han M, Chen X. The prognostic impact of preoperative CA19-9 on resectable cholangiocarcinoma: a comprehensive systematic review and meta-analysis. Discov Oncol. 2024;15(1):773. 10.1007/s12672-024-01683-w.
21. Izquierdo-Sanchez L, Lamarca A, La Casta A, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol. 2022;76(5):1109–21. 10.1016/j.jhep.2021.12.010.
22. Maithel SK, Keilson JM, Cao HST, et al. NEO-GAP: A Single-Arm, Phase II Feasibility Trial of Neoadjuvant Gemcitabine, Cisplatin, and Nab-Paclitaxel for Resectable, High-Risk Intrahepatic Cholangiocarcinoma. Ann Surg Oncol. 2023;30(11):6558–66. 10.1245/s10434-023-13809-5.
23. Yuan ZB, Fang HB, Feng QK, Li T, Li J. Prognostic factors of recurrent intrahepatic cholangiocarcinoma after hepatectomy: A retrospective study. World J Gastroenterol. 2022;28(15):1574–87. 10.3748/wjg.v28.i15.1574.
24. Cillo U, Fondevila C, Donadon M, et al. Surgery for cholangiocarcinoma. Liver Int. 2019;39(Suppl 1):143–55. 10.1111/liv.14089.
25. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019;20(5):663–73. 10.1016/S1470-2045(18)30915-X.

26. Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 1992;117(3):215–20. 10.7326/0003-4819-117-3-215.
27. Runyon BA. Malignancy-related ascites and ascitic fluid humoral tests of malignancy. J Clin Gastroenterol. 1994;18(2):94–8. 10.1097/00004836-199403000-00002.

Tables

Table 1. Baseline characteristics by baseline ascites

Variable	Baseline ascites (n=55)	No baseline ascites (n=140)	p
Age, years - median [IQR]	65.3 [61.1–71.0]	64.7 [55.8–70.6]	0.370
Male sex, n (%)	31 (56.4)	85 (60.7)	0.578
HBsAg positive, n (%)	24 (44.4)	58 (42.0)	0.761
HCV positive, n (%)	5 (9.4)	20 (14.7)	0.337
Alcoholism, n (%)	3 (8.1)	10 (11.9)	0.752
eCCA (vs iCCA), n (%)	2 (3.6)	9 (6.5)	0.731
Combined HCC, n (%)	10 (19.6)	31 (23.7)	0.556
Late stage (III–IV), n (%)	22 (40.0)	30 (21.6)	**0.009**
Microvascular invasion, n (%)	42 (76.4)	90 (64.7)	0.118
Macrovascular invasion, n (%)	5 (9.4)	12 (8.7)	1.000
CA19-9, U/mL - median [IQR]	63.7 [25.6–419.0]	22.3 [11.2–91.4]	**0.001**
AFP, ng/mL - median [IQR]	4.1 [2.6–11.2]	3.3 [2.1–7.2]	0.207
Albumin, g/dL - median [IQR]	4.0 [3.6–4.2]	4.1 [3.8–4.3]	0.083
Total bilirubin, mg/dL - median [IQR]	0.7 [0.5–1.1]	0.6 [0.5–1.0]	0.486
ALP, U/L - median [IQR]	94 [66.8–151.5]	86.5 [64.0–111.0]	0.142
ALT, U/L - median [IQR]	25.0 [20.5–39.5]	28.0 [19.0–47.0]	0.798
AST, U/L - median [IQR]	32.0 [26.0–42.5]	30.0 [23.0–44.2]	0.683
Platelet, /µL - median [IQR]	182000 [143000–229500]	186500 [157500–245250]	0.267
INR - median [IQR]	1.1 [1.0–1.1]	1.1 [1.0–1.1]	0.492
Sodium, mmol/L - median [IQR]	140 [139–141]	140 [139–142]	0.195
Creatinine, mg/dL - median [IQR]	0.8 [0.7–1.0]	0.8 [0.7–1.0]	0.688
ALBI score - median [IQR]	−2.7 [−2.9, −2.3]	−2.8 [−3.0, −2.5]	**0.045**
Cirrhosis (ISHAK>4), n (%)	15 (27.3)	32 (22.9)	0.517
FIB-4 >2.67, n (%)	19 (34.5)	42 (30.9)	0.623

Table 2. Overall survival with ascites as a time-dependent covariate (n=195, 88 deaths)

Model	Variable	HR (95% CI)	p
A. Any ascites (time-dependent)	Ascites present	3.59 (2.27–5.70)	**<0.001**
B. Baseline vs incident (unadjusted)	Baseline ascites	2.78 (1.65–4.69)	**<0.001**
	Incident ascites (time-dependent)	5.21 (3.06–8.90)	**<0.001**
C. Adjusted (multiple imputation, n=195)	Baseline ascites	1.94 (1.12–3.38)	**0.018**
	Incident ascites (time-dependent)	3.24 (1.81–5.80)	**<0.001**
	Age ≥65	1.44 (0.92–2.24)	0.107
	Clinical stage (per stage)	1.19 (0.95–1.49)	0.133
	ALBI grade 2/3	2.14 (1.33–3.44)	**0.002**
	CA19-9 >38 U/mL	2.03 (1.26–3.27)	**0.003**

Table 3. Risk factors for baseline ascites (logistic regression; n=195, 55 events)

Variable	Univariable OR (95% CI)	p	Multivariable OR (95% CI)†	p
CA19-9 >38 U/mL	2.84 (1.47–5.50)	**0.002**	2.22 (1.10–4.49)	**0.027**
Clinical stage (per stage)	1.59 (1.16–2.19)	**0.004**	1.40 (1.00–1.96)	**0.049**
ALP >100 U/L	1.68 (0.88–3.22)	0.114	-	-
Microvascular invasion	1.76 (0.86–3.59)	0.120	-	-
HCV positive	0.60 (0.21–1.70)	0.340	-	-
ALBI grade 2/3	1.35 (0.72–2.52)	0.353	-	-
eCCA (vs iCCA)	0.55 (0.11–2.61)	0.447	-	-
Cirrhosis (ISHAK>4)	1.27 (0.62–2.58)	0.517	-	-
Combined HCC	0.79 (0.35–1.75)	0.557	-	-
Male sex	0.84 (0.44–1.57)	0.578	-	-
FIB-4 >2.67	1.18 (0.61–2.30)	0.623	-	-
HBsAg positive	1.10 (0.59–2.08)	0.761	-	-
Age ≥65	1.10 (0.59–2.05)	0.769	-	-
Macrovascular invasion	1.09 (0.37–3.27)	0.873	-	-

Table 4. Risk factors for incident ascites (cause-specific Cox regression; n=138, 57 events)

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)†	p
Clinical stage (per stage)	1.95 (1.50–2.54)	**<0.001**	1.60 (1.14–2.26)	**0.007**
ALP >100 U/L	2.93 (1.69–5.08)	**<0.001**	1.98 (0.99–3.97)	0.054
CA19-9 >38 U/mL	2.90 (1.63–5.17)	**<0.001**	1.44 (0.73–2.82)	0.289
Macrovascular invasion	4.43 (1.87–10.48)	**<0.001**	4.56 (1.75–11.90)	**0.002**
ALBI grade 2/3	2.14 (1.26–3.65)	**0.005**	1.65 (0.92–2.96)	0.096
Cirrhosis (ISHAK>4)	2.13 (1.21–3.76)	**0.009**	1.50 (0.81–2.79)	0.199
Microvascular invasion	2.18 (1.19–4.00)	**0.011**	1.18 (0.57–2.45)	0.661
Combined HCC	0.62 (0.31–1.24)	0.173	-	-
FIB-4 >2.67	1.47 (0.84–2.55)	0.176	-	-
eCCA (vs iCCA)	1.72 (0.62–4.79)	0.299	-	-
HCV positive	0.79 (0.36–1.75)	0.564	-	-
Male sex	1.15 (0.67–1.97)	0.603	-	-
HBsAg positive	0.87 (0.51–1.49)	0.619	-	-
Age ≥65	1.04 (0.61–1.75)	0.894	-	-

Figures

Figure 1. Patient flow chart

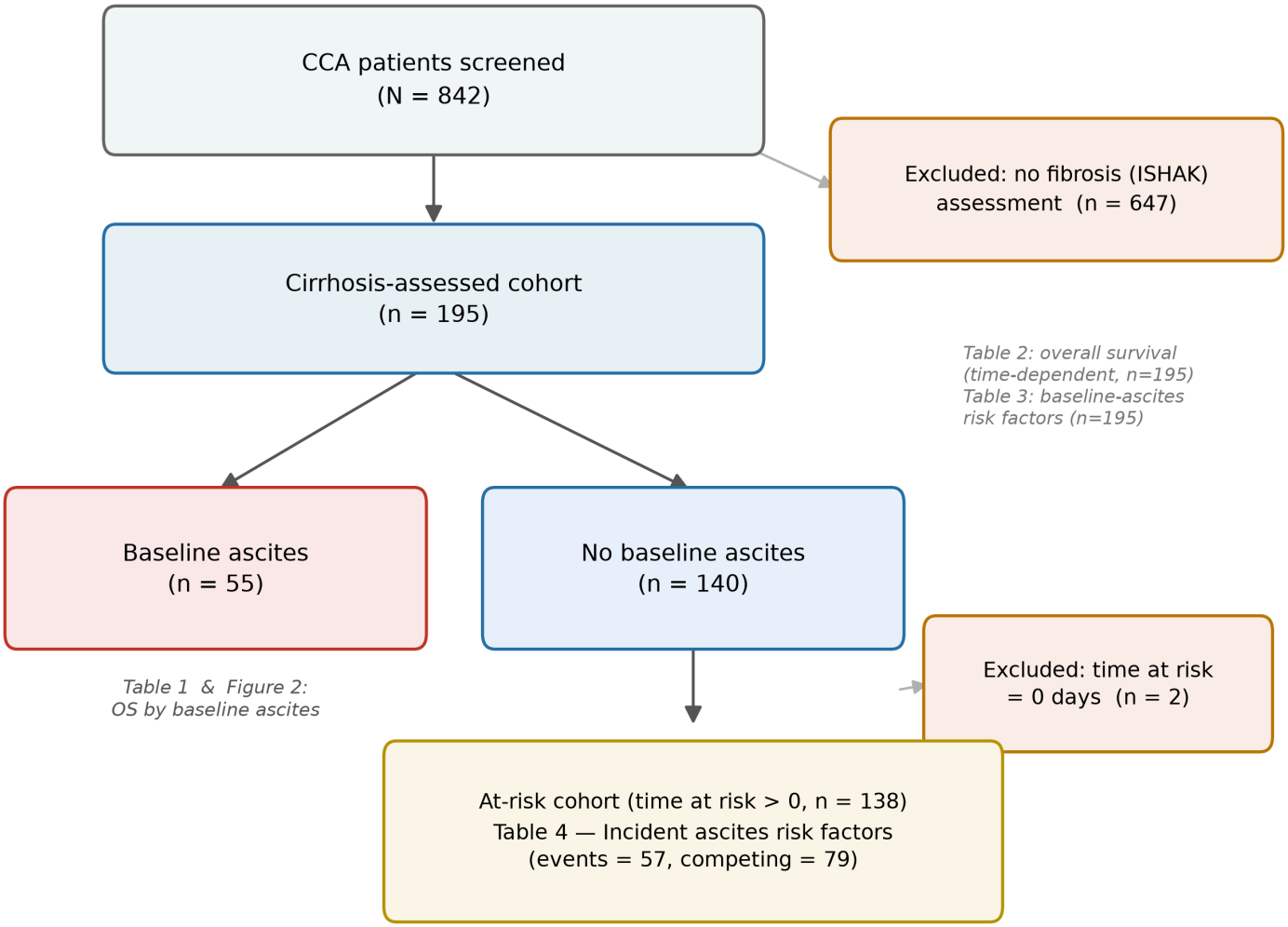


Figure 1

Patient flow chart.

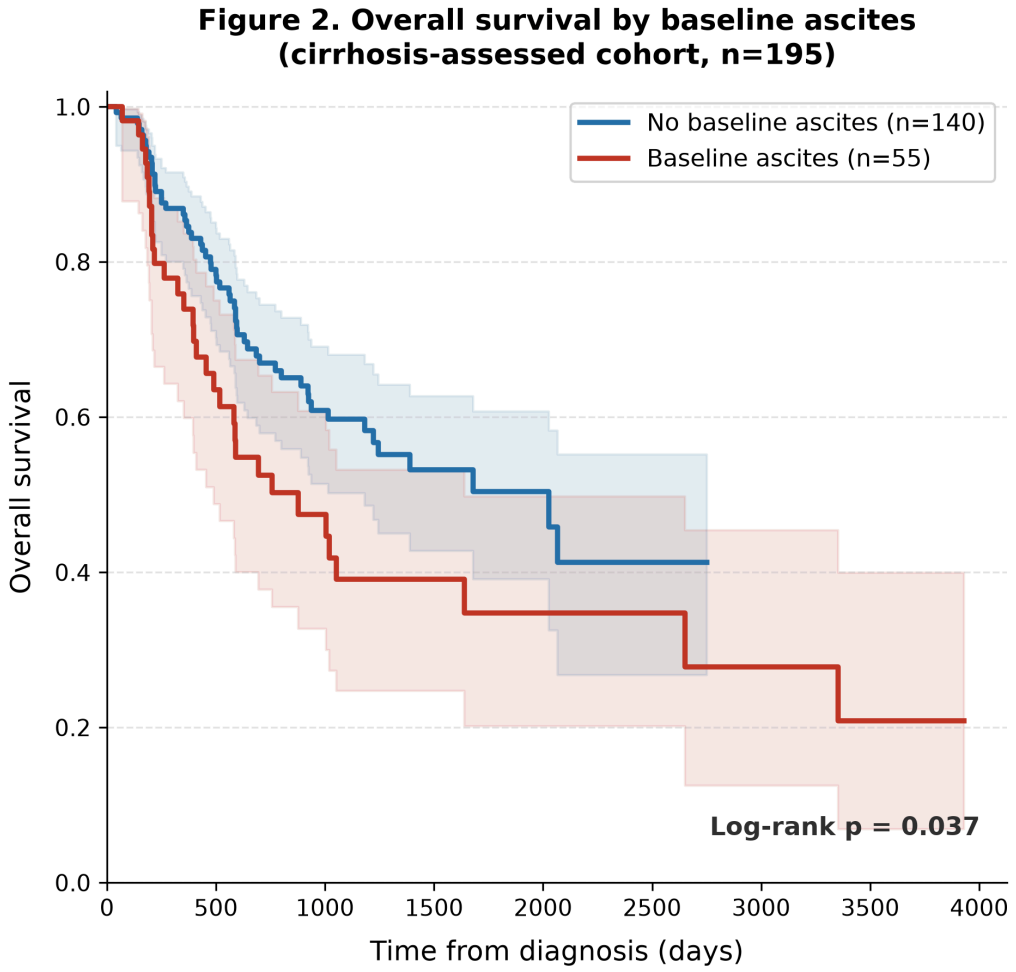


Figure 2

Overall survival by baseline ascites (cirrhosis-assessed cohort, n=195).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 06STROBEchecklist.docx