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ORIGINAL ARTICLE

T2 gallbladder cancer shows substantial survival variation between continents and this is not due to histopathologic criteria or pathologic sampling differences

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Abstract

Published data on survival of T2 gallbladder carcinoma (GBC) from different countries show a wide range of 5-year survival rates from 30–> 70%. Recently, studies have demonstrated substantial variation between countries in terms of their approach to sampling gallbladders, and furthermore, that pathologists from different continents apply highly variable criteria in determining stage of invasion in this organ. These findings raised the question of whether these variations in pathologic evaluation could account for the vastly different survival rates of T2 GBC reported in the literature. In this study, survival of 316 GBCs from three countries (Chile $n = 137$, South Korea $n = 105$, USA $n = 74$), all adequately sampled (with a minimum of five tumor sections examined) and histopathologically verified as pT2 (after consensus examination by expert pathologists from three continents), was analyzed. Chilean patients had a significantly worse prognosis based on 5-year all-cause mortality (HR: 1.89, 95% CI: 1.27–2.83, $p = 0.002$) and disease-specific mortality (HR: 2.41, 95% CI: 1.51–3.84, $p < 0.001$), compared to their South Korean counterparts, even when controlled for age and sex. Comparing the USA to South Korea, the survival differences in all-cause mortality (HR: 1.75, 95% CI: 1.12–2.75, $p = 0.015$) and disease-specific mortality (HR: 1.94, 95% CI: 1.14–3.31, $p = 0.015$) were also pronounced. The 3-year disease-specific survival rates in South Korea, the USA, and Chile were 75%, 65%, and 55%, respectively, the 5-year disease-specific survival rates were 60%, 50%, and 50%, respectively, and the overall 5-year survival rates were 55%, 45%, and 35%, respectively. In conclusion, the survival of true T2 GBC in properly classified cases is neither as good nor as bad as previously documented in the literature and shows notable geographic differences even in well-sampled cases with consensus histopathologic criteria. Future studies should focus on other potential reasons including biologic, etiopathogenetic, management-related, populational, or healthcare practice-related factors that may influence the survival differences of T2 GBC in different regions.

Keywords Gallbladder cancer · Tumor staging · Survival

Introduction

Incidence rates of gallbladder carcinoma (GBC) demonstrate pronounced geographic, ethnic, racial, and cultural variations [1–5]. In general, GBC is rare in Western countries (below 3 per 100,000/year in women and 1.5 per 100,000/year in men) and is more common in some parts of South America and Asia [1–3, 6–9]. Cancer-related mortality parallels this pattern, with GBC representing the fourth leading cause of cancer-related deaths among Chilean women [10], but contributing to relatively few deaths in North America and Northern Europe [1, 2, 6].

In the literature, marked geographic variation in the prognosis of GBC in different regions is reported. The 5-year survival rates of T2 GBC, defined as invasion into perimuscular tissue but not the serosa or liver, vary tremendously, and range from 30% in the USA-based SEER (Surveillance Epidemiology End Results) database, to over 70% in the Far East [5, 6, 8, 11–33]. Recently, this marked variation in reported survival has been partly attributed to differences in the

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approaches and criteria applied in the pathologic evaluation and staging of GBC employed in different countries, namely, variations in (1) tumor sampling and (2) histopathologic interpretation. Extensive sampling of the gallbladder is performed in Chile and the Far East even if there are no gross anatomic or pathologic (naked-eye) findings [34, 35]. In contrast, there is a far less extensive sampling of gallbladders in the West, with some even advocating that it may not even be necessary to examine gallbladders histologically when gross anatomic or pathologic findings are absent [36–41]. Limited gallbladder sampling in the West has led to under-staging of disease that is only visible microscopically [42, 43]. Furthermore, GBC is notoriously subtle, with infiltration patterns that tend to be clinically and radiographically indistinct, causing more than half of GBCs to be undiagnosed pre-operatively in the West [12, 44–46]. Lack of adequate histological examination often leads to sub-standard examination of gallbladder specimens in pathology laboratories [42, 47–49].

Separately, recent international consensus studies have highlighted another important pathology-related factor contributing to geographic variation in T2 GBC survival: the high variation in the histopathologic assessment of pathologic stage among experts from different continents. Among 12 experts from seven countries, substantial variations were also discovered in the evaluation of the depth of invasion of GBC (the manuscripts regarding these findings are in preparation [50, 51]), akin to the differences observed for gastric cancers [52, 53].

In order to determine whether microscopic pathologic criteria and gross anatomic sampling could account for the reported geographic survival differences of T2 GBC, adequately sampled cases from different regions were evaluated by an international group of experts through consensus meetings and slide sharing.

Materials and methods

Study population

The analysis dataset included 316 GBC cases from eight collaborating institutions in three countries. All cases were verified to be stage pT2 through an international consensus and only cases with more than five tumor slides that were sampled grossly were included (see below).

Information on patient demographic characteristics (sex, age at diagnosis, and country of residence), diagnosis date, follow-up duration, and vital status at follow-up was obtained from the medical records. Vital status was defined using the following categories: alive, death of GBC, death of secondary disease related to GBC (e.g., peritoneal carcinomatosis), death of another disease, and death of unknown cause. Vital status information was available through January 2017. The diagnosis dates ranged from 1987 to 2015.

Pathology data collection

Microscopic pathology slides of cholecystectomy specimens were reviewed for convincing perimuscular invasion without extension to the serosa or into the liver (pT2). Only cases with a sampling of at least five tumor sections were included in the study. On average, seven tumor sections per case were available for review. Gallbladder specimens from Chile and South Korea were submitted entirely for microscopic examination, which is routine practice in those countries [34], whereas many of the USA cases were not completely sampled.

Consensus meetings were held in Seoul, South Korea, in 2016, and Santiago, Chile, in 2017, along with slide sharing through telepathology. The extent of invasion for each case was then classified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for GBC. Cases representing carcinoma in situ (pT*is*) colonizing Rokitansky-Aschoff sinuses, which can mimic T2 GBC, were carefully excluded (Fig. 1a). Tumors that invaded into the lamina propria or muscularis without overt penetration into the perimuscular fibrous tissue (pT1) were also excluded (Fig. 1b). Finally, cases demonstrating involvement of the serosal and/or hepatic surfaces (pT3) were also omitted (Fig. 1c). Histologic type and grade were also denoted.

Data analysis

Kaplan-Meier curves and the corresponding log-rank tests were used to compare survival across the three countries. Multivariable Cox proportional hazard analysis was performed to further examine the association between geographic location and survival after adjusting for sex and age at diagnosis (≤ 60 years, 61–70 years, and > 70 years), and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) and p values were reported. The multivariable survival analyses were conducted for both all-cause and GBC-specific mortality. For GBC-specific mortality, the event of interest was defined as death from GBC or from secondary disease related to GBC. The proportional hazards assumption was tested for all variables in the models by inspecting the log-log curves; none violated the proportional hazards assumption. Two-way interactions were tested by including cross-products for a geographic site with sex and age. The standard statistical software package SPSS (version 23 for Windows; IBM Corp., Armonk, NY) was used to analyze the data. The cutoff for statistical significance was set at the two-sided alpha error of 0.05.

Results

Table 1 presents the demographic and pathologic characteristics of the T2 GBC cases by geographic cohort. Women represented the majority of study participants (73%) but varied in proportion depending on geographic location. While the female/male ratio in Chile was 6.7, it was only 2.3 in the USA and 1.3 in South Korea. The study sample was equally distributed across age categories, and this age distribution was generally similar across the three countries. All cases were fundamentally adenocarcinomas but there were other components present in a small percentage (adenosquamous 2%, signet ring cell 2.5%, neuroendocrine 2.5%, sarcomatoid/undifferentiated 2.5%, medullary pattern 1%, and others 1.6%), and the frequency of the histologic types did not differ significantly across the three geographic regions. In terms of tumor grading, overall, 61% of cases from all geographic regions were grade 2 and the cases from South Korea and the USA were more likely to be lower grade at diagnosis compared with the cases from Chile, which were much more frequently grade 2 at diagnosis ($p < 0.001$, chi-squared test). The presence of a tumoral intraepithelial neoplasm component (i.e., pyloric gland adenoma, or intracholecystic papillary neoplasm, or as collectively also referred to as intracholecystic papillary tubular neoplasm) was not specifically evaluated in this international consensus study, partly also due to the differences in approaches in the classification and terminology of such lesions; the consensus review was focused on the T2 component of the carcinomas.

Hazard ratios for all-cause and GBC-specific mortality are presented in Tables 2 and 3. No significant interactions were present. After controlling for age and sex, patients from the USA and Chile had higher mortality compared to patients from South Korea (HR: 1.75, 95% CI: 1.12–2.75, $p = 0.02$ and HR: 1.89, 95% CI: 1.27–2.83, $p = 0.002$, respectively). The observed difference further increased in the analyses of GBC-specific mortality with adjusted HRs (95% CI, p values) of 1.94 (1.14–3.31, $p = 0.02$) and 2.41 (1.51–3.84, $p < 0.001$) for the USA and Chile (relative to South Korea), respectively. After controlling for study site, age at diagnosis and patient sex were unrelated to survival in all analyses.

Upon 1-year follow-up, the survival differences were particularly pronounced between South Korea and Chile (85% and 70%, respectively) while survival in the USA was in-between (80%). By 3 years of follow-up, the difference between Chile and the USA was no longer evident (50% and 55%, respectively), and overall survival was significantly higher (70%) in South Korea. The overall 5-year survival of T2 GBC was 45%. However, this varied significantly by geographic site, with South Korea consistently demonstrating the highest survival across the entire follow-up period (Fig. 2). The 5-year overall survival remained similar between Chile and the USA (45% and 35%, respectively), but was still significantly higher in South Korea (55%).

The differences in disease-specific survival were generally similar to those seen with overall survival (Fig. 3). At 1 year of follow-up, disease-specific survival was virtually equivalent in South Korea and the USA (90% and 85%, respectively),

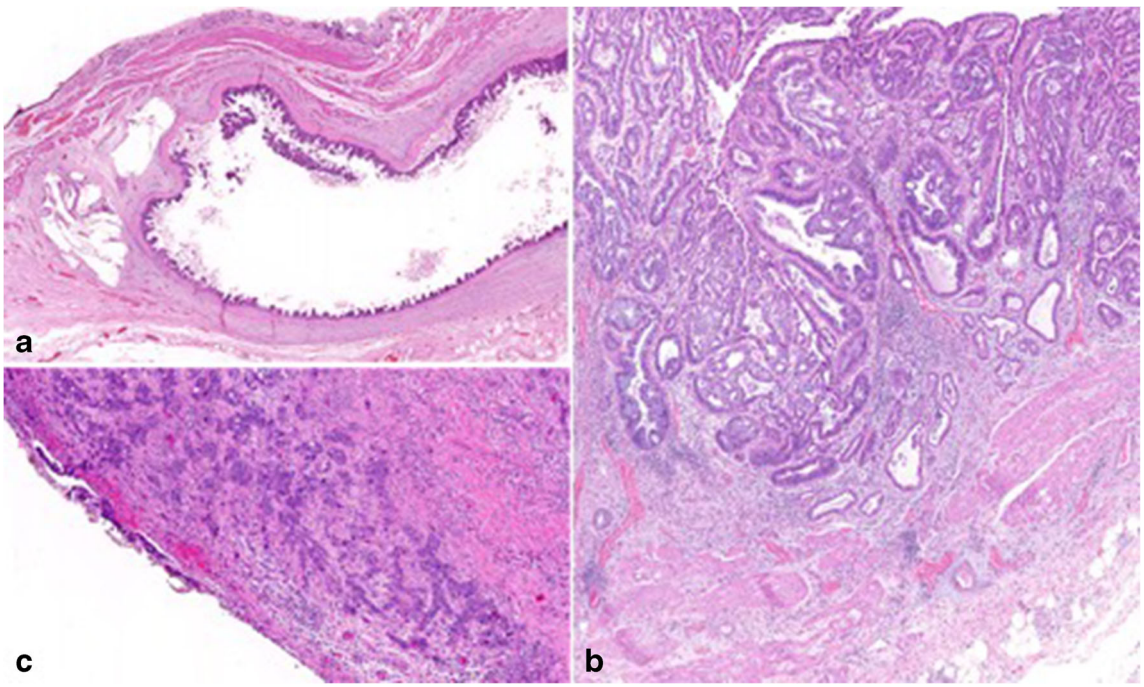

Fig. 1 Excluded cases. **a** Carcinoma in situ (pT*is*) that colonized Rokitansky-Aschoff sinuses, which can mimic T2 carcinomas, **b** cases of tumor that invaded into the lamina propria or muscularis without growth into the perimuscular fibrous tissue (pT1), and **c** cases with involvement of the serosal and/or hepatic surface (pT3)

Table 1 Demographic characteristics of patients with T2 GBC from collaborating institutions

Patient characteristic		Geographic Region, *n* (%)			
		USA, *n* = 74	Chile, *n* = 137	South Korea, *n* = 105	Total, *n* = 316
Sex	Female	52 (70)	119 (87)	59 (56)	230 (73)
	Male	22 (30)	18 (13)	46 (44)	86 (27)
Age, years	≤ 60	27 (36)	39 (28)	35 (33)	101 (32)
	61–70	24 (32)	45 (33)	36 (34)	105 (33)
	> 70	23 (31)	53 (39)	34 (32)	110 (35)
Tumor type	Adenocarcinoma	64 (86)	110 (80)	100 (95)	274 (87)
	NEC + AdenoCA	2 (3)	-	2 (2)	4 (1)
	NEC + medullary CA	-	2 (1)	-	2 (0.6)
	Pure NEC	-	2 (1)	-	2 (0.6)
	Signet ring cell CA	1 (1)	7 (5)	-	8 (2.5)
	Medullary CA	2 (3)	2 (1)	-	4 (1)
	Sarcomatoid/Undiff. CA	2 (3)	4 (3)	2 (2)	8 (2.5)
	Other	3 (4)	10 (7)	1 (1)	14 (4.4)
Tumor grade*	1	20 (27)	4 (3)	34 (32)	58 (19)
	2	31 (42)	107 (78)	49 (47)	187 (61)
	3	12 (16)	21 (15)	19 (14)	52 (17)
	4	2 (3)	5 (4)	2 (2)	9 (3)

CA, carcinoma; *NEC*, neuroendocrine carcinoma, *Undiff*, undifferentiated

whereas survival in Chile was only 70%. By 3 years of follow-up, the geographic differences between disease-specific survival were more pronounced: South Korea had the highest survival (75%), followed by the USA (65%), and then Chile (55%). As the duration of follow-up increased to 5 years after diagnosis, the disease-specific survival curves in Chile and the USA converged at 50%, which was significantly lower than survival in South Korea (70%).

Recent cases, i.e., cases that were diagnosed after 2000, had significantly better overall and disease-specific 5-year survival rates (53% and 67%, respectively) than the earlier cases (35% and 40%, respectively); however, the distribution of the cases throughout the cohort (between 1987 and 2015) was not equally distributed for the three countries to compare.

Discussion

The current impression in the literature on survival of GBC is mostly based on the Surveillance Epidemiology End Results (SEER) database, managed by the USA National Cancer Institute [20, 54, 55], which is notoriously unreliable for staging, because the data received from throughout the country is provided without standardized sampling or interpretation and without central review. Publications from institutional data, on the other hand, are mostly derived from surgical datasets, which suffer from the relatively infrequent pathologic verification for pathologic processing. Therefore, it is not surprising that there are vastly different data regarding the survival of T2

Table 2 Multivariable survival analyses assessing independent associations of age, sex, and geographic region with 5-year all-cause mortality among T2 GBC patients

Variables		HR (95% CI)	*p* value
Geographic region	South Korea	Reference	
	USA	1.75 (1.12–2.75)	0.015
	Chile	1.89 (1.27–2.83)	0.002
Sex	Female	Reference	
	Male	1.37 (0.95–1.97)	0.096
Age, years	≤ 60	Reference	
	61–70	1.10 (0.72–1.68)	0.652
	> 70	1.34 (0.90–2.01)	0.152

Table 3 Multivariable survival analyses assessing independent associations of age, sex, and geographic region with 5-year disease-specific mortality among T2 GBC patients

Variables		HR (95% CI)	*p* value
Geographic region	South Korea	Reference	
	USA	1.94 (1.14–3.31)	0.015
	Chile	2.41 (1.51–3.84)	< 0.001
Sex	Female	Reference	
	Male	1.34 (0.88–2.04)	0.171
Age, years	≤ 60	Reference	
	61–70	1.25 (0.78–2.00)	0.358
	> 70	1.24 (0.78–1.99)	0.361

GBC, ranging from 30 to 70%, even in the SEER database and institutional USA cohorts produce highly variable survival rates [2, 5, 6, 8, 11–33].

The results of this study, the largest, international, multi-institutional cohort of centrally reviewed and well-sampled cases, demonstrate that in cases with pT2 GBC confirmed through international consensus pathologic diagnosis, the overall 5-year survival of T2 GBC is 45%, and the disease-specific survival is 55%. These figures are, on the one hand, significantly higher than most reported using the SEER database but, on the other hand, are substantially lower than those reported in the Far East.

This study also supports that the survival differences reported for GBC patients from South Korea, Chile, and the USA are not attributable to pathologic sampling and histopathologic interpretative differences, since both of these were controlled in this study. The difference in survival between countries was most striking in the 3-year disease-specific survival rates, which were 75%, 65%, and 55%, for South Korea, the USA, and Chile, respectively. The survival advantage of the South Korean cohort was maintained over the course of follow-up although the survival of Chilean and USA patients started to merge over time.

Previously, it had been speculated that the higher GBC survival rates reported in South Korea could be explained partly by the differences in the criteria used to determine invasiveness, especially over-staging of T*is* cases that colonized Rokitansky-Aschoff sinuses, mimicking pT2 GBC. This impression was based on geographic differences in frequency of the T*is* and T1 GBC which were highlighted in recent consensus meetings [51]. These geographic differences are similar to those reported for gastric cancers [52, 53]. However, even in this study where the T2 stage was verified through international consensus agreement, these survival differences persisted.

Additionally, in this study, only cases with at least five tumor sections were included in the analysis so as to minimize the potential impact of under-sampling (and thus under-staging) of tumors. The Chilean GBC patients had the lowest survival rates, despite all cases being entirely sampled for microscopic examination, and despite careful verification of T-stage by authors from other regions. Thus, inadequate sampling cannot explain the regional survival differences we observed.

This study was able to exclude the two main pathology-related factors implicated as sources of the survival differences reported for T2 GBC: (1) geographic differences in the application of pathologic T-staging criteria and (2) under-sampling phenomenon leading to under-staging. Accordingly, the differences in survival appear to be attributable to pathologic or biologic characteristics other than T-stage, such as different tumor characteristics, healthcare practices such as post-operative management, or regional differences in prognostic risk factors, and the pathogenesis of GBC [2, 5, 12, 56, 57].

It is conceivable that some of the geographic variations in GBC survival are related to the variable prevalence of certain etiopathogenetic factors. Studies have shown that GBC is far more frequent in Chilean and American women than men, while the female/male ratio is much lower in Korea. This difference in female/male ratio was confirmed in our study, where Chile had the highest female/male ratio (6.7), followed

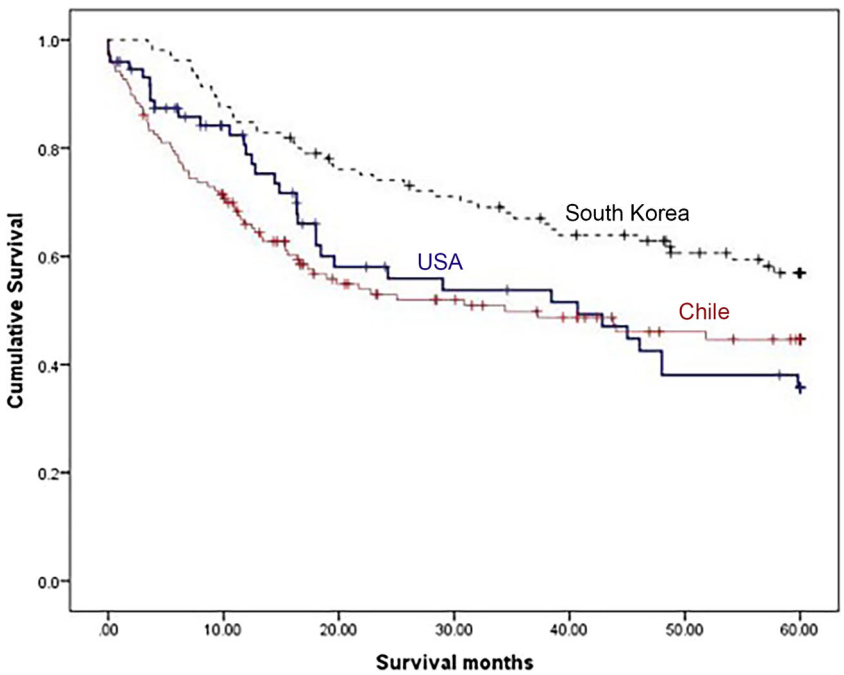

Fig. 2 Kaplan-Meier curve of 1-year, 3-year, and 5-year overall survival for T2 GBC patients (n = 316) by geographic cohort

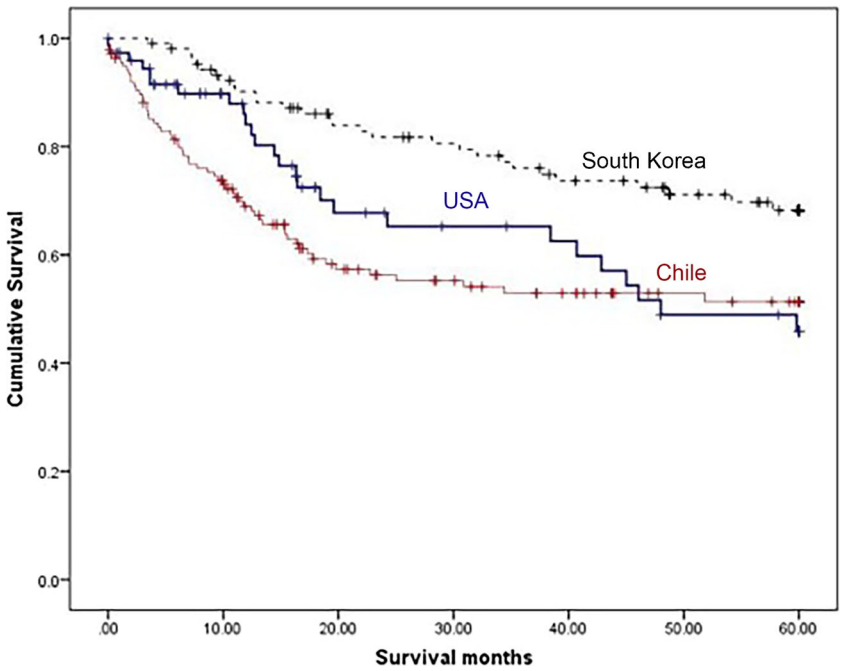

Fig. 3 Kaplan-Meier curve of 1-year, 3-year, and 5-year disease-specific survival for T2 GBC patients (n = 316) by geographic cohort

by the USA (2.3) and Korea (1.3). In some studies, female sex and advanced age have been found to be associated with more invasive disease and worse prognosis [2, 3, 6, 8, 58–60]. However, patient sex and age were not independent prognostic factors in our analyses.

Additionally, the frequency of gallstones in the general population as well as in patients with GBC has been reported to be much higher in Chile than in the Far East. Along those lines, the duration of biliary calculus disease and mutations in regulatory genes *KRAS* and *TP53* have been shown to vary by populations, as reported in the literature [2, 5, 12, 57]. Several other studies also demonstrate region-specific mutational profiles that may account for the geographic differences of GBC. One large multi-institutional international study compared cancer-specific mutations in GBC tumor samples from patients treated in Chile, Japan, and the USA, and identified *TP53* and *SMAD4* as the most commonly mutated genes across the cohort while, at the same time, demonstrating some region-specific driver mutations: *ARID1A* or *PIK3CA* mutations were absent in the Japanese patient cohort, and *ERBB3* mutations were absent in the Chilean patient cohort [61]. Yang et al. [62] performed next-generation sequencing on GBC tumors in over 200 Chinese and USA patients and found that genetic alterations in the *ERBB* pathway were more frequent in the Chinese patients than that in their USA counterparts. Moreover, Chinese patients with GBC more frequently demonstrated DNA repair genetic aberrations, lending further evidence to support geographic differences in the drivers of gallbladder carcinogenesis. In addition, a recent exome-sequencing study [63] supported the precursor lesion intracholecystic papillary neoplasm (ICPN) as a genetically and clinicopathologically distinct entity from papillary and nonpapillary GBC, with mutations in *STK11*, *CTNNB1*, and *APC* identified as the common drivers, which may also contribute to geographic differences.

These observations raise the possibility of etiopathogenetic factors other than gallstones contributing to GBC carcinogenesis in some countries, which may then account for part of the behavioral differences. For example, in the Far East, close to 10% of GBC is attributed to a reflux-related carcinogenesis induced by pancreaticobiliary maljunction (supra-Oddi/anomalous union of the common bile duct and main pancreatic duct), allowing the escape of pancreatic enzymes into the gallbladder and biliary tree and causing cancer in those sites [64–68]. It is possible that more cases in the Far East may be related to a similar non-gallstone-related phenomenon even in the absence of pancreaticobiliary maljunction. One may speculate that gallstone-associated GBC, which accounts for the vast majority of GBCs in Chile where gallstones are prevalent and detected in greater than 90% of the cases, may be more aggressive considering that inflammation-related cancers in other organs also have worse outcomes than their sporadic counterparts [69]. Along those lines, the presence and type of the pre-invasive neoplasm, which have been shown to confer distinct biologic characteristics to invasive carcinomas (including differences in molecular pathways involved) may also exhibit variation by geography and thus may be a factor in the survival differences detected in this study. Similarly, in our analysis, the grade of the invasive carcinomas appeared to be lower in the USA and Korea than in Chile. These and other pathologic factors (other than sampling and T-stage interpretation which are now excluded by the results of this study) need to be further investigated.

Naturally, some of the geographic variation in GBC survival among the included countries is also attributable, at least in part, to access to different management protocols, including surgery, chemotherapy, and/or radiotherapy. The cases in our study were identified in the pathology databases of the authors' institutions, many of the patients were consultations that were originally managed at other institutions, and, as a result, much of the clinical information other than survival data was not accessible to the authors. Thus, treatment was not controlled in this study, which is common practice in other studies of rare cancer types as well. Future studies should focus on clinical and surgical practices, as well as on different mechanisms of carcinogenesis that may affect the survival differences noted in different geographic regions.

Author contribution statement All authors agreed with the content and gave explicit consent to submit this work. All authors made substantial contributions to the conception, design, case acquisition, analysis, and interpretation of data, and assisted with drafting and revising the work, approving the version to be published. The authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study involved 3 continents and investigators from 5 countries and entailed the collection and detailed re-review of clinical and pathology findings in hundreds of gallbladder cancer patients, with multiple consensus meetings held in Santiago, Chile; Atlanta, USA; and Seoul, Korea. Each investigator contributed significantly in multiple ways as outlined below:

NVA, JK, JCR, MDR, OB, and JYJ conceived the study and designed the approach and analytic methods along with MSDS and MG. Case procurement for study, case organization, and collection of clinical information including survival data were performed by JMS and SKM from the USA, HFL and JCA from Chile, and JYJ, KTJ, and SHM from Korea. Initial histopathologic review in different continents was conducted by SMH, KL, HK, HJC, and KTJ (Korean cases), NVA, BP, BM, MDR, and OB (for cases from the USA), and JCA, JCR, and EB (for Chilean cases). The international pathology consensus meetings were organized and coordinated by JCR (in Santiago, Chile), JCA (in Temuco, Chile), JYJ and KTJ (in Seoul, Korea), and NVA and JK (in Atlanta, USA), and the working group that conducted the re-review of the pathology material included JYJ, SKL, HK, HJC, SMH, and KTJ, from Korea, NVA, OB, MDR, JK, from the USA, and JCR, JCA, EB, and HL from Chile. TM, BP, and BM performed the organization of the combined international data. MSD, BP, BM, MDR, TM, OB, JK, and NVA conducted the literature analysis and organization of the manuscript. Statistical analysis was performed by MG, MSDS, JK, and SB. MSDS, MG, OB, MDR, JK, and NVA prepared the manuscript draft. All authors of this paper have critically reviewed the intellectual content and approved the final version submitted.

Compliance with ethical standards

The study was conducted in accordance with the Institutional Review Board requirements.

Conflict of interest The authors declare that they have no conflict of interest.

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The manuscript has not been submitted to more than one journal for simultaneous consideration. The submitted work is original and has not been published elsewhere in any form. This study has not been split up into several parts to increase the quantity of submissions. Results presented herein have been done so without fabrication, falsification, or inappropriate data manipulation. Others' work has been properly acknowledged in the references.

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