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Keywords
Prognosis, Diagnosis, Survival, Cholecystectomy, : Gallbladder cancer

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Introduction
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Material and methods
Sixty-five patients diagnosed with GBC between January 1, 2016, and June 30, 2023, were evaluated for age, gender, laboratory parameters, treatment, diagnosis time, follow-up, survival, and pathological results. Estimated life expectancy and survival rate were calculated, and demographic findings, imaging, pathology, and laboratory results were compared as a function of survival and diagnostic time.

Results
Roughly three quarters of the patients (73.8%) were female; the mean age of the cohort was 65.6±11.9 years (range: 24–93 years). About one third (29.2%) of the patients were diagnosed preoperatively. A statistically significant difference between the groups was detected in terms of priority treatment, tumor differentiation, tumor dimensions, and ALP results. Poor differentiation, high T stage, and high CEA and GGT values were statistically significantly different in the patients who died. Based on univariate analysis, we found that CRP, elevated CAR, low and moderate differentiation, T2, T3, and T4 were all risk factors. On the other hand, elevated ALB was determined to be a protective factor.

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Keywords: Gallbladder cancer, Cholecystectomy, Diagnosis, Prognosis, Survival.

INTRODUCTION

Gallbladder cancer (GBC) is the fifth most common cancer of the digestive system, with an incidence rate of roughly 3 per 100,000 individuals. This cancer is observed in 0.2–3.0% cases of open cholecystectomy (OC) but 0.09–2.00% cases of laparoscopic cholecystectomy (LC). Only 30% of GBC cases are detected prior to surgery, and surgical operation is possible in only 15–47% of cases [1].

While the overall survival rate of GBC is 5%, this rate increases to 75% in early-stage cancers. T-stage, lymph node involvement, metastasis, and jaundice have been reported as GBC prognostic factors [2]. Although increased age, an urban lifestyle, complaints of jaundice, the presence of cholelithiasis and liver involvement, and advanced tumor stage have all been reported as poor prognostic factors of GBC, surgery and radiotherapy have been reported to be protective factors [3].

Tumor markers are used in the follow-up of recurrence and treatment rather than diagnosis in many cancers. In the case of GBC, CEA sensitivity (specificity) was reported to be 11.7% (97.4%) and CA19-9 sensitivity (specificity) was reported to be 71.7% (96.1%). When assessing tumor stage, lymph node involvement, and recurrence, CEA was found to have no impact on prognosis; CA19-9 was identified to be a significant prognostic factor. Recently, CAR and mGPS, derived from acute-phase reactants such as CRP and albumin, have been used to predict prognosis in various types of cancer, including GBC. Considering the time of diagnosis, patients with suspected cancer prior to surgery have been reported to have poor survival rates [4-7].

Here, we evaluated how the timing of diagnosis affects the prognosis and survival rates of patients with GBC.

MATERIAL AND METHOD

After the decision of the Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Committee (İstanbul, Türkiye) dated July 31, 2023, and numbered 122, the charts of patients over the age of 18 who were diagnosed with GBC between January 1, 2016, and June 30, 2023, were retrospectively reviewed. Patients younger than 18 years old or patients who had other hepatopancreatobiliary cancers were excluded from the study.

Demographic data of the patients such as age, gender, treatment priority (surgical or oncological), type of surgery, time of diagnosis, duration of follow-up (days), and survival status (right or dead) were reviewed retrospectively. The type of surgery categorized as laparoscopic cholecystectomy (LC), open cholecystectomy (OC), laparoscopic cholecystectomy + extra surgical intervention (LC+ES), open cholecystectomy + extra surgical intervention (OC+ES), right or left hepatectomy (H), or diagnostic laparoscopy (DL). The time of diagnosis was categorized as preoperative (PROP), peroperative (PEROP), or postoperative (PSOP). Due to the small number of patients in some groups, PROP and

PEROP patients were grouped together as PREOP. Pathological results were reviewed retrospectively regarding pathological diagnosis, T stage, and differentiation.

The laboratory results of carcinoembryonic antigen (CEA) (µg/L), the cancer antigen 19-9 (CA19-9) (kU/L), alanine transferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), alkaline phosphatase (ALP) (U/L), gamma-glutamyl transferase (GGT) (U/L), total/direct bilirubin (TBİL, DBİL) (mg/dL), C-reactive protein (CRP) (mg/L), albumin (ALB) (g/L), CRP/ALB ratio (CAR), white blood cells (WBC) (10^3/uL), hemoglobin (HB) (g/L), and platelets (PLT) (10^3/uL) were reviewed retrospectively.

Estimated lifetime (median [SE], 95% CI) and survival rate (1, 2, 3, 5, and 10 years [SE]) were calculated retrospectively.

According to survival status (DEAD/ALIVE), gender, age, priority treatment, follow-up period, type of surgery, diagnosis time, imaging, pathology, and laboratory results were compared.

Gender, age, follow-up period, type of surgery, imaging, pathology, total follow-up period, survival (1, 2 and 5 years), laboratory results, estimated life expectancy and survival (1, 2, 3, 5, and 10 years (SE)) were compared according to the time of diagnosis (PREOP/PSOP).

The factors that determine the survival of the patients were analyzed using univariate and multivariate Cox Regression analysis.

Statistical Analysis

SPSS 15.0 (IBM, NY, USA) for Windows was used for the statistical analysis. Descriptive statistics included numbers and percentages for categorical variables and averages, standard deviations, minimums, maximums, and medians for numerical variables. The ratios in the groups were compared using a Chi-Squared test. Numerical variables between two independent groups were compared using the Student's t-test when the normality condition was met and the Mann-Whitney U test when it was not. Survival rates, Kaplan-Meier analysis, and risk factors were examined using Cox Regression analysis. Statistical significance was presumed for a p level below 0.05.

RESULTS

Sixty-five patients were included in our study. Roughly one third of them (26.2%; n=17) were male and 73.8% (n=48) were female. The mean age of the patients was 65.6±11.9 years (range: 24–93 years). The majority of the patients (84.6%; n=55) were primarily treated surgically, whereas 15.4% (n=10) were treated oncologically. While 10.8% of the patients (n=7) were not operated on, LC was applied in 29.2% of cases (n=19), OC in 20.0% of cases (n=13), LC+ES in 7.7% of cases (n=5), OC+ES in 21.6% of cases (n=14), right/left hepatectomy in 6.2% of cases (n=4), and TL in 4.6% of cases (n=3). Roughly one third of the patients (29.2%; n=19) were diagnosed with PEROP, while 70.8% (n=46) were diagnosed with PSOP. Gallbladder cancer was detected in 0.51% (46 out of 9,000) of patients who

underwent cholecystectomy. The mean follow-up duration was 36.7±43. months. While 73.8% (n=48) of the patients had died by DATE, 26.2% (n=17) were alive (Table 1).

The pathology most often detected with adenocarcinoma (89.2%; n=58) and mixed carcinoma (3.1%; n=2). Tumor stages included T2 (30.8%; n=20), T3 (23.1%; n=15), T4 (18.5%; n=12), and T1 (13.8%; n=9). Tumor differentiation was determined to be moderate in 54.4% of cases (n=36), well in 29.2% of cases (n=19), and low in 15.4% of cases (n=10) (Table 1).

Mean CEA was 12.3±31.0 µg/L, mean CA19-9 was 740.5±2641.4 kU/L, mean ALT was 75.5±201.1 U/L, mean AST was 105.9±403.1 U/L, mean ALP was 158.9±136.5 U/L, mean GGT was 139.7±229.6 U/L, mean TBL was 1.81±3.51 mg/dL, mean DBIL was 1.03±2.20 mg/dL, mean CRP was 65.3±104.5 mg/L, mean ALB was 3.58±0.66 g/L, mean CAR was 21.8±36.9, mean WBC was 11.7±10.9 10^3/uL, mean HB was 11.8±1.6 g/L, and mean PLT was 262.7±89.5 10^3/uL (Table 2).

The patients' mean estimated life expectancy was 18.7±3.1 months. The 1-year survival rate was 63.6%, the 2-year survival rate was 44.9%, the 3-year survival rate was 35.9%, the 5-year survival rate was 23.7%, and the 10-year survival rate was 20.3% (Table 3).

A little more than half of the patients in the PREOP group were female (63.2%; n=12); 78.3% (n=36) of the patients in the PSOP group were female. The mean age of the PREOP group was 64.2±12.6 years, while the mean age of the PSOP group was 69.8±8.9 years. There was no statistically significant difference between the groups in terms of gender or age (p=0.228 and p=0.157, respectively). While oncological treatment was the priority for 52.6% (n=10) of patients in the PREOP group, surgery was applied to all patients (100%) in the PSOP group. There was a statistically significant difference between the groups regarding priority treatment (p=0.001). As a form of surgery, TL and hepatectomy were applied only to the PREOP group. On the other hand, other types of surgery were used more in the PSOP group, and this difference between the two groups was found to be statistically significant (p<0.001). There was no statistically significant difference between the two groups regarding adenocarcinoma or other pathological diagnoses (p=0.063). Roughly one third (31.6%; n=6) of the patients in the PREOP group and 8.7% (n=4) of the patients in the PSOP group exhibited less-differentiated tumors. There was a statistically significant difference between the groups regarding differentiation (p=0.043). The T stage of the PREOP group was mostly T3 and T4; 84.2% (n=16) of patients fell into that category. The T stage of the patients in the PSOP group was mostly T1 and T2 (73.9%; n=34). There was a statistically significant difference between the groups regarding T phase (p<0.001). The mean total follow-up period of the PREOP group was 62.4±9.7 months; the mean total follow-up period of the PSOP group was 67.0±12.6 months. There was no statistically significant difference between the groups regarding total follow-up period and 1-, 2-, and 5-year follow-up periods (p=0.082). While 78.9% (n=15) of the patients in the PREOP group had died , 71.7% of the patients in

the PSOP group during follow-up periods. Although the mortality rate was higher in the PREOP group, the difference was not statistically significant (p=0.758) (Table 1).

Based on laboratory findings segregated according to time of diagnosis, CEA, CA 19-9, ALP, GGT, total bilirubin (TBIL), DBIL, WBC, and PLT were higher in the PREOP group; ALT, AST, CRP, ALB, CAR, and HB were higher in the PSOP group. The only statistically significant difference was for ALP, however (p=0.015; Table 2).

There were no statistically significant differences in patient survival rates or life expectancy at diagnosis (p=0.108; Table 3).

Based on laboratory findings segregated according to survival, CEA, CA 19-9, ALP, GGT, TBIL, DBIL, CRP, CAR, WBC, and PLT were higher in deceased patients; ALT, AST, ALB, and HB were higher in living patients. However, only the CEA and GGT differences were statistically significant (p=0.025 and p=0.049, respectively; Table 4).

According to univariate Cox Regression Analysis, the factors determining patient survival included CRP (p=0.016), elevated CAR (p=0.009), low and medium differentiation (p<0.001), T2 (p=0.001), T3 (p=0.003), and T4 (p<0.001); elevated ALB was a protective factor (p=0.040; Table 5).

However, multivariate analyses failed to reveal any significant risks associated with mortality for any of these factors (p=0.685). The multivariate model showed that elevated CAR, minimal and medium differentiation risk factors, and elevated CRP were reducing factors (p=0.03, 0.025, 0.002, and 0.003, respectively; Table 6).

DISCUSSION

While the overall survival rate of GBC is 5%, it increases to 75% in early-stage cancers [8]. Rakić et al. showed that T-phase, lymph node involvement, metastasis, and jaundice were prognostic factors of GBC [1]. Similarly, Feroz et al. showed that increased age, an urban life, jaundice complaints, a presence of cholelithiasis, liver involvement, advanced tumor stage, advanced clinical stage, and advanced TNM stage were prognostic factors of GBC. Surgery and radiotherapy have also been identified as protective factors [2]. Additionally, Fujiwara et al. reported that patients with suspected preoperative cancer had low survival rates [3]. In this study, we investigated the effect of time of diagnosis on prognosis.

Miura et al. showed that the 5-year overall survival rate of GBC was 34.5% [4]. Feroz et al. showed the general median survival duration was 5 months; the general annual survival rates to 1, 2, and 3 years were 24.4%, 8.5%, and 4.5%, respectively [3]. Gourgiotis et al. reported an average survival period of 9.2 months for patients suspected of having preoperative GBC; that number can be compared with an average of 26.5 months for patients identified incidentally postoperatively [5]. In our study, the average patient life expectancy was determined to be 18.7 months. This average patient life expectancy was

13.2 months in patients in the PREOP group and 21.9 months in patients in the PSOP group. While the survival time of our patients with suspected cancer was longer than that reported in the literature, the average survival time of patients diagnosed incidentally postoperatively was shorter than that noted in the literature. The annual survival rates we noted are higher than those reported in the literature; we found rates of 63.6%, 44 %, 35.9%, 23.7%, and 20.3% at 1, 2, 3, 5, and 10 years, respectively. In terms of the time of diagnosis, the 5-year survival rate of patients suspected of having cancer was 9.1%; individuals diagnosed postoperatively had a significantly higher rate (i.e., 28.6%). Additionally, the 10-year survival rate for postoperative cases was determined to be 23.8%.

Feroz et al. found that the 1-year survival rate for individuals aged 26–45 was 40%; the three-year survival rate for the same age cohort dropped to 6.7%. For patients aged 46–65, the average 1-year survival rate was 19.1%; the average 3-year survival rate was just 3.8%. Increased age was identified as a negative prognostic factor [3]. Cui reported survival rates for patients over 65: 63.1% at six months, 42.9% at one year, and 20% at three years. A similar group of patients over 65 exhibited slightly different rates of 62.7%, 32%, and 16.9%, respectively; however, the differences were not statistically significant [6]. Miura et al. found that the average survival duration for patients under 65 years old was 14 months; that cohort's average 5-year overall survival rate was 24%.

On the other hand, patients over 65 exhibited a mean survival duration of 27.3 months and a five-year survival rate of 45%. Although these figures are higher than those reported in other literature, they are not significantly different from literature-noted values [4]. Alarabiyat et al. reported that the average age of patients with cancer detected incidentally was 63 years, compared with an average age of 66 years for patients with suspected cancer. That difference highlights the significant impact of age on overall survival [9]. Similarly, Altıok and colleagues found an average age of 62 years among patients detected incidentally; survival differences based on age—above or below 60—were not significant, that team noted [10]. In our study, we observed that the mean age of deceased patients was 64.2 years; living patients had a mean age of 69.8 years . Notably, the average age of patients with incidentally detected cancer was also 69.8 years; patients with suspected cancer had an average age of 64.2 years. Ultimately, our findings indicated that age did not significantly affect survival outcomes, regardless of the general cohort or the timing of the diagnosis.

Females are at a 2–6-fold greater risk for developing GBC than males [1]. Miura et al. showed that the average survival duration for men was 14.9 months, with a 5-year overall survival rate of 29%. On the other hand, women had an average survival duration of 23.6 months and a 5-year overall survival rate of 34%. While a female gender is considered a high risk factor for GBC, Miura et al. found no statistically significant difference in prognosis between genders [4]. Alarabiyat et al. reported that a GBC detection rate among women of 84% for individuals identified incidentally and 68% for individuals with suspected GBC; however, these findings were not statistically significant concerning overall survival [8]. In our study, we found that 75% of deceased patients and 70.6% of living patients

were female. Among those patients diagnosed incidentally, 78.3% were women, and 63.2% of patients with suspected cancer were also female. Ultimately, we observed no significant effect of gender on overall survival.

Feroz et al. reported that adenocarcinomas accounted for 89.8% of GBC cases. The survival rates for patients with adenocarcinomas were 22.8%, 7.6%, and 5.1% at one, two, and three years, respectively. On the other hand, the survival rates for patients without adenocarcinomas were 38.9%, 16.7%, and 0% for the same time intervals [2]. Alarabiyat et al. found that 94% of adenocarcinomas were detected in patients undergoing surgery; that cohort included individuals suspected of having cancer or whose cancer was identified incidentally [9]. Similarly, Altıok et al. reported a detection rate of 92.5% for adenocarcinomas in patients with cancer identified incidentally; those authors noted no statistically significant effect on overall survival [10]. In our study, adenocarcinoma was found in 87% of patients diagnosed incidentally and 94.7% of patients with suspected cancer. Among deceased patients, adenocarcinoma was present in 91.7% of cases; 82.4% of the overall cohort had a diagnosis of adenocarcinoma. Although the rate of adenocarcinoma was lower in patients who survived and were detected incidentally postoperatively, we found no significant difference in overall survival associated with an absence of adenocarcinoma.

Alarabiyat et al. reported that 35% of GBC cases were detected postoperatively, while 65% were identified following suspicion of the disease. The timing of diagnosis was found to have a statistically significant impact on overall survival [9]. Cha et al. reported that 41.8% of GBC cases were detected incidentally postoperatively; 58.2% were identified in patients with suspected cancer. Among those patients in that study diagnosed incidentally, 72.7% were alive, compared with only 30.4% of those with suspected cancer. That difference was statistically significant. Furthermore, the mean survival duration for patients with cancer detected incidentally was 13.2 months; it was only 6.8 months for patients suspected of having cancer. This difference was also statistically significant, indicating that diagnostic timing significantly affects overall survival [11]. However, our study revealed a different trend: 70.8% of GBC cases were detected incidentally postoperatively, with GBC found in only 0.21% of patients undergoing cholecystectomy. While 28.3% of patients diagnosed incidentally experienced cancer, just 21.1% of patients with suspected cancer experienced cancer. The average survival duration for patients detected incidentally was 21.9 months, compared with 13.2 months for patients with suspected cancer. Despite the longer survival durations associated with incidental detection, our study concluded that the timing of diagnosis did not significantly affect overall survival.

Feroz et al. reported that 43.3% of GBC patients underwent surgery. The general survival rates for patients who were not operated on were 13.3%, 0%, and 0%, respectively, at 1, 2, and 3 years. For patients who were operated on, the corresponding rates were 61.0%, 36.6%, and 19.5%, respectively. This difference was statistically significant [2]. Cha et al. reported that 21.7% of patients suspected of having cancer underwent surgery; this difference was also statistically significant [11]. In our study, all

patients detected incidentally underwent surgery; 47.4% of patients suspected of having cancer were operated on. A statistically significant decrease in the rate of surgery was observed in patients with suspected GBC. However, no significant effect on overall survival was detected.

Feroz et al. reported that 59.7% of GBC cases were well or moderately differentiated. The overall survival rates at 1, 2, and 3 years for patients with well or moderately differentiated tumors were 34.3%, 13.3%, and 6.7%, respectively. On the other hand, patients with poorly differentiated tumors exhibited corresponding survival rates of 9.4%, 1.4%, and 1.4%, respectively [2]. Alarabiyat et al. showed that 64% of cancers detected incidentally were well or moderately differentiated; 76% of cancers in patients with suspected cancer were well or moderately differentiated. However, differentiation did not significantly impact overall survival [9]. In our study, 79.2% of deceased patients and all of the surviving patients had well or moderately differentiated tumors. Among patients with cancer detected incidentally, 91.3% had well or moderately differentiated tumors, compared with 68.4% in patients with suspected cancer. Statistically speaking, better differentiation in incidentally detected tumors was associated with improved survival in living patients and after surgery.

There have been many reports in the literature that T stage is one of the most important prognostic factors for GBC [5, 12]. Forez et al. showed that 28.4% of GBC cases were classified as T1/T2. The 1-, 2-, and 3-year overall survival rates for T1/T2 cancers were 54%, 26%, and 16%, respectively; T3/T4 cancers, the corresponding rates were 12.7%, 1.6%, and 0%, respectively. The higher survival rates associated with T1/T2 cancers were statistically significant [2]. Alarabiyat et al. noted that 84% of incidentally detected cases were T1/T2, compared with 41% of cases with suspected cancer. The lower T stage in incidentally detected cases was statistically significant, and the T stage was found to have a significant impact on overall survival [9]. In our study, 82.3% of the surviving patients and 47.9% of the deceased patients were classified as having T1/T2 cancer. Among the incidentally detected cases, 73.9% were T1/T2, compared with 15.8% in patients with suspected cancer. The higher proportion of T1/T2 cases and their prognostic significance were statistically significant in surviving and incidentally detected patients.

Tumor markers are often used in the follow-up of recurrence and treatment rather than for diagnosis in many cancers. Wang et al. showed that the sensitivity of CEA was 11.7%, with a specificity of 97.4%; the sensitivity of CA19-9 was 71.7%, and its specificity was 96.1% for GBC. CEA was not clinically significant when evaluated regarding tumor stage, lymph node involvement, or recurrence; CA19-9 was identified as an important prognostic factor [13]. In another study by Cui et al., patients with a CEA value less than 3.02 had overall survival rates of 67.6%, 51.4%, and 30.7%, respectively, at 6 months, 1 year, and 3 years. Those numbers can be compared with 58.8%, 25.9%, and 8.2% in patients with a CEA value above 3.02. Those differences were statistically significant. In the same study, patients with CA19-9 levels less than 142.95 had overall survival rates of 61.5%, 39.6%, and 23.8%, respectively, at 6 months, 1 year, and 3 years. Patients with CA19-9 levels greater than 142.95 had corresponding

survival rates of 65.1%, 34.9%, and 10.9%, respectively. Those differences were not statistically significant [14]. In our study, CEA values were significantly higher in patients who died compared with individuals who survived; CEA values were also higher in patients with suspected cancer than in individuals with incidental findings. However, the prognostic effect of elevated CEA was not observed. Similarly, CA19-9 levels were higher in deceased patients and in individuals with suspected cancer compared with individuals with incidentally detected cancer. However, the prognostic effect of elevated CA19-9 was not detected.

Jaundice has been reported in numerous studies to be an indicator of GBC inoperability and poor prognosis [2, 15, 16]. Mishra et al. reported an average bilirubin level of 5 mg/dL in GBC patients [16]. Similarly, Feroz et al. reported 1-, 2-, and 3-year overall survival rates for patients without jaundice of 34.7%, 12.5%, and 6.9%, respectively. On the other hand, the corresponding survival rates for patients with jaundice were 17.3%, 5.8%, and 2.9%, respectively. The presence of jaundice was found to have a statistically significant effect on prognosis [2].

In our study, the mean TBIL in deceased patients was 2.12±4.09 mg/dL, compared with 1.00±0.61 mg/dL in surviving patients and 3.37±5.67 mg/dL in patients with suspected cancer. However, no significant effect on survival was observed. Consistent with the literature, we found that bilirubin values were higher in deceased patients. We suggest that the lower bilirubin levels in patients with incidentally detected cancer may indicate a better prognosis for this group.

Acute-phase reactants, such as CRP, ALB), and the C-reactive protein-to-albumin ratio (CAR), as well as the modified Glasgow Prognostic Score (mGPS), have been increasingly used to predict prognosis in various cancers, including GBC [17, 18]. Utsumi et al. reported a mean CRP level in GBC patients of 1.58±3.38 mg/dL and a mean albumin level of 3.84±0.66 g/dL. These same authors noted that CAR greater than or equal to 0.07 was associated with poor prognosis [17]. In our study, mean CRP, ALB, and CAR values were 75.2±116.5 mg/L, 3.49±0.67 g/L, and 25.5±41.6, respectively, in deceased patients; the corresponding values in surviving patients were 39.6±60.5 mg/L, 3.80±0.58 g/L, and 12.2±18.7, respectively. Patients with suspected cancer exhibited values of 58.0±69.0 mg/L, 3.30±0.56 g/L, and 19.5±24.4, respectively. We found that CRP significantly affected ALB and CAR in terms of prognosis. Consistent with the literature, our study suggests that elevated CAR indicates poor prognosis in deceased patients. Interestingly, unlike other prognostic factors, elevated CAR in patients with incidentally detected cancer may be related to acute inflammation.

In conclusion, GBC is a rare cancer with a poor prognosis. We noted a difference in prognosis between patients diagnosed before or during surgery and patients with cancer detected incidentally via postoperative pathology. The literature suggest that patients diagnosed with GBC before or during surgery generally have a poorer prognosis than patients with cancer found incidentally postoperatively. Although we observed a difference in prognosis based on the timing of diagnosis, that difference was

not statistically significant. We believe that the timing of diagnosis is an important factor in prognosis, with an earlier diagnosis—particularly before or during surgery—being associated with poorer outcomes, including poor differentiation, advanced T stage, high CA19-9 levels, elevated bilirubin values, and lower 5-year survival rates. Prospective, randomized, multicenter studies with larger patient populations are necessary to validate the statistical significance of our findings.

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Patient consent for publication

Not obtained because the study was retrospective.

Competing interests

All authors declare no conflict of interest.

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- Only 30% of GBC cases are detected prior to surgery, and surgical operation is possible in only 15–47% of cases
- T-stage, lymph node involvement, metastasis, and jaundice have been reported as GBC prognostic factors
- Considering the time of diagnosis, patients with suspected cancer prior to surgery have been reported to have poor survival rates
- Timing of diagnosis is an important factor in prognosis, with an earlier diagnosis—particularly before or during surgery—being associated with poorer outcomes, including poor differentiation, advanced T stage, high CA19-9 levels, elevated bilirubin values, and lower 5-year survival rates

Table 1: Demographic and Pathological Findings

		TOTAL		PREOP		PSOP		*p*
		n	%	n	%	n	%	
Gender	Male	17	26,2	7	36,8	10	21,7	0,228
	Woman	48	73,8	12	63,2	36	78,3	
Age* (years)		65,6±11,9 (24-93)		64,2±12,6 24-93 (65)		69,8±8,9 51-82 (72)		0,157k
Priority Treatment	Surgery	55	84,6	9	47,4	46	100	**0,001**
	Oncology	10	15,4	10	52,6	0	0	
Type of Surgery	No surgery	7	10,8	7	36,8	0	0	**<0,001**
	LC	19	29,2	0	0	19	40	
	OC	13	20	2	10,5	11	24,4	
	LC+ASI	5	7,7	0	0	5	11,1	
	OC+ASI	14	21,6	3	15,8	11	24,5	
	Right/Left Hepatectomy	4	6,2	4	30,1	0	0	
	DL	3	4,6	3	15,8	0	0	
Time of Diagnosis	PEROP	19	29,2					
	PSOP	46	70,8					
Follow-up Period ** (months)		36,7±43,0 1,2-184,9 (17,6)		62,4±9,7 45-79 (60)		67,0±12,6 24-93 (67)		0.082b
Survival	Dead	48	73,8	15	78,9	33	71,7	0,758
	Alive	17	26,2	4	21,1	13	28,3	
Pathology	Adenocarcinoma	58	89,2	18	94,7	40	87	0,663
	Mixt Carcinoma	2	3,1					
	Pleomorphic sarcoma	1	1,5					
	Lymphoma	1	1,5					
	BilIN	1	1,5	1	5,3	6	13	
	In situ carcinoma	1	1,5					
	Adenosquamous Carcinoma	1	1,5					
T Stage	T1	9	13,8					**<0,001**
	T1A	3	4,6	2	10,5	15	32,6	
	T1B	5	7,7					
	T2	20	30,8	1	5,3	19	41,3	
	T3	15	23,1	9	47,4	6	13	
	T4	12	18,5	7	36,8	6	13	
	T4A	1	1,5					
Differentiation	Poor	10	15,4	6	31,6	4	8,7	**0,043**
	Middle	36	55,4	3	15,8	16	34,8	
	Good	19	29,2	10	52,6	26	56,5	

*** Mean±SD (Min-Max) ** Mean±SD Min-Max (Median) LC: laparoscopic cholecystectomy, OC: open cholecystectomy, ASI: adjunctive surgical intervention, DL: diagnostic laparoscopy, PEROP: pre-peroperative diagnosis, PSOP: postoperative diagnosis, BilIN: biliary intraepithelial neoplasia, T: tumor size (TNM classification)**

Table 2: Laboratory Findings

	TOTAL		PREOP		PSOP		p^b
	Mean±SD	**Min-Max**	**Mean±SD**	**Min-Maks (Median)**	**Mean±SD**	**Min-Maks (Median)**	
CEA	12,3±31,0	1,06-151	12,6±26,7	1,08-95 (2,625)	12,2±33,7	1,06-151 (2,24)	0,614
CA19-9	740,5±2641,4	0,8-13275	779,2±2366,5	0,8-8274 (25,15)	719,4±2833,6	0,8-13275 (11,78)	0,288
ALT	75,5±201,1	6-1301	52,6±72,1	6-241 (18)	86,5±240,6	7-1301 (21)	0,876
AST	105,9±403,1	12-2664	56,6±68,7	16-259 (21)	129,6±489,7	12-2664 (23)	0,659
ALP	158,9±136,5	54-765	228,6±198,9	85-765 (146)	125,2±77,3	54-373 (99)	**0,015**
GGT	139,7±229,6	15-1016	215,7±341,6	25-1016 (59)	103,0±143,4	15-734 (64)	0,271
TBIL	1,81±3,51	0,20-21,4	3,37±5,67	0,20-21,40 (0,92)	1,06±1,29	0,28-7,17 (0,68)	0,055
DBIL	1,03±2,20	0,06-11,6	2,03±3,33	0,08-11,60 (0,28)	0,53±1,11	0,06-6 (0,24)	0,378
CRP	65,3±104,5	0,79-527	58,0±69,0	2-243 (36)	68,7±118,8	0,79-527 (26)	0,551
ALB	3,58±0,66	1,6-4,9	3,30±0,56	2,60-4,40 (3,15)	3,71±0,67	1,60-4,90 (3,70)	0.056 $^{\alpha}$
CAR	21,8±36,9	0,2-195,2	19,5±24,4	0,5-86,8 (10,7)	22,9±42,0	0,2-195,2 (7,3)	0,476
WBC	11,7±10,9	3,9-74	14,8±17,9	3,9-74 (10,8)	10,2±4,6	5,3-20,6 (8,9)	0,856
HB	11,8±1,6	8,3-16,2	11,7±2,0	8,3-15,4 (11,7)	11,9±1,4	9,2-16,2 (11,8)	0,785
PLT	262,7±89,5	65-499	267,4±118,0	96-499 (243)	260,5±74,4	65-468 (263)	0.845 $^{\beta}$

CEA: carcinoembryogenic antigen (µg/L), CA19-9: cancer antigen 19-9 (kU/L), ALT: alanine transferase (U/L), AST: aspartate aminotransferase (U/L), ALP: alkaline phosphatase (U/L), GGT: gamma glutamyl transferase (U/L), TBIL, DBIL: total/ direct bilirubin (mg/dL), CRP: C reactive protein (mg/L), ALB: albumin (g/L), CAR: CRP/ALB ratio, WBC: white blood cell (10^3/uL), HB: hemoglobin (g/L), PLT: platelet (10^3/uL) α Student's t Test β Mann Whitney U Test

Table 3: Estimated Life Expectancy, Survival Rates

	TOTAL		PREOP		PSOP	
	Median (SE)	95% CI	Median (SE)	95% CI	Median (SE)	95% CI
Estimated Life Expectancy	18,7 (3,1)	12,7-24,8	13,2 (3,7)	6-20,5	21,9 (5,5)	11,1-32,8
Survival Rate (%)	1-year 63.6% (SE:6.1)		1-year 54.4% (SE:12.0)		1-year 67.0% (SE:7.0)	
	2- year 44% (SE:6.3)		2-year 30.2% (SE:11.2)		2-year 49.1% (SE:7.4)	
	3-year 35.9% (SE:6.1)		3-year 18.1% (SE:9.4)		3-year 40.2% (SE:7.3)	
	5-year 23.7% (SE:5.5)		5-year 9.1% (SE:8.0)		5-year 28.6% (SE:6.8)	
	10-year 20.3% (SE:5.7)				10-year 23.8% (SE:7.1)	

Table 4: Demographic, Pathology and Laboratory Findings Based on Patient Survival

		Survival				
		Dead		Alive		
		n	%	n	%	p[#]
Gender	Male	12	25	5	29,4	0,754
	Woman	36	75	12	70,6	
Age*		64,2±12,6		69,8±8,9		0.096 [α]
		24-93 (65)		51-82 (72)		
Follow-up Time *		19,4±18,0		85,5±54,8		**<0,001 [β]**
		1,2-98,1 (13,0)		8,1-184,9 (75,1)		
Type of Surgery	LC	12	28,6	7	43,8	0,586
	OC	10	23,8	3	18,8	
	LC+ASI	5	11,9	0	0	
	OC+ASI	6	14,3	4	25	
	OC+Liver	4	9,5	0	0	
	Right/Left Hepatectomy	3	7,1	1	6,3	
	DL	2	4,8	1	6,3	
Time of Diagnosis	PREOP	15	78,9	4	21,1	0,22
	PSOP	33	71,7	13	28,3	
Pathology	Adenocarcinoma	44	91,7	14	82,4	0,366
	Other	4	8,3	3	17,6	
Differentiation	Poor	10	20,8	0	0	**0,004**
	Middle	29	60,4	7	41,2	
	Good	9	18,8	10	58,8	
T Stage	T1	6	12,5	11	64,7	**0,001**
	T2	17	35,4	3	17,6	
	T3	14	29,2	1	5,9	
	T4	11	22,9	2	11,8	
		Mean±SD	Min-Maks (Median)	Mean±SD	Min-Maks (Median)	p [b]
CEA		16,73±36,18	1,06-151 (2,905)	1,84±0,46	1,08-2,59 (1,83)	**0,025**

CA19-9	1042,3±3112,4	0,8-13275 (21,25)	16,1±16,4	0,83-46,4 (9,15)	0,196
ALT	48,8±66,7	6-264 (21)	144,4±367,6	12-1301 (19,5)	0,82
AST	48,0±58,9	12-259 (23)	255,4±759,7	14-2664 (23,5)	0,659
ALP	176,8±153,8	60-765 (118)	112,7±58,3	54-274 (103)	0,254
GGT	171,9±262,6	18-1016 (66)	56,5±51,4	15-197 (36,5)	**0,049**
TBIL	2,12±4,09	0,28-21,4 (0,71)	1,00±0,61	0,20-2,37 (0,84)	0,759
DBIL	1,26±2,52	0,09-11,6 (0,23)	0,39±0,35	0,06-1,24 (0,27)	0,844
CRP	75,2±116,5	1,28-527 (30)	39,6±60,5	0,79-210 (13)	0,211
ALB	3,49±0,67	1,6-4,9 (3,6)	3,80±0,58	2,6-4,4 (3,85)	0.171[α]
CAR	25,5±41,6	0,3-195,2 (8,4)	12,2±18,7	0,2-61,8 (3,4)	0,192
WBC	12,3±12,6	3,9-74 (8,9)	10,2±4,1	5,7-20,04 (8,9)	0,8
HB	11,7±1,5	8,3-14,2 (12)	12,2±2,0	9,6-16,2 (11,75)	0,8
PLT	274,0±88,0	96-499 (270)	233,7±90,6	65-439 (233,5)	0.188 [α]

***Mea.±SD Min-Max (Median) LC: laparoscopic cholecystectomy, OC: open cholecystectomy, ASI: additional surgical intervention, DL: diagnostic laparoscopy, PEROP: pre-peroperative diagnosis, PSOP: postoperative diagnosis, T: tumor size (TNM classification) CEA: carcinoembryogenic antigen (µg/L), CA19-9: cancer antigen 19-9 (kU/L), ALT: alanine aminotransferase (U/L), AST: aspartate aminotransferase (U/L), ALP: alcaline phosphatase (U/L), GGT: gamma glutamyl transferase (U/L), TBIL, DBIL: total/ direct bilirubin (mg/dL), CRP: C reactive protein (mg/L), ALB: albumin (g/L), CAR: CRP/ALB ratio, WBC: white blood cell (10^3/uL), HB: hemoglobin (g/L), PLT: platelet (10^3/uL) #Ki Square Test [α] Student's t Test [β] Mann Whitney U Test**

Table 5: Univariate Cox Regression Analysis of Factors Determining Patients' Survival

		p	HR	95% CI	
Age		0,687	0,995	0,969	1,021
Gender (Ref: Male) Female		0,218	1,511	0,784	2,913
Priority treatment (Ref: Surgery) Oncology		0,148	1,717	0,825	3,572
Time of diagnosis (Ref: PEROP) PSOP		0,112	0,605	0,326	1,124
CEA		0,457	1,004	0,993	1,015
CA19-9		0,23	1	1	1
ALT		0,4	0,999	0,997	1,001
AST		0,369	0,999	0,997	1,001
ALP		0,111	1,002	1	1,004
GGT		0,105	1,001	1	1,002
TBIL		0,222	1,049	0,971	1,132
DBIL		0,094	1,113	0,982	1,262
CRP		**0,016**	1,004	1,001	1,007
ALB		**0,04**	0,552	0,314	0,972
CAR		**0,009**	1,012	1,003	1,021
WBC		0,235	1,022	0,986	1,06
HB		0,297	0,897	0,73	1,101
PLT		0,091	1,004	0,999	1,008
Pathology (Ref: Adenocarcinoma) Other		0,492	1,434	0,513	4,005
Differentiation (Ref: Good differentiation)		**<0,001**			
	Poor	**<0,001**	5,911	2,317	15,075
	Middle	**0,001**	3,756	1,761	8,008
T Stage (Ref:T1)		**<0,001**			
	T2	**0,003**	4,221	1,651	10,792
	T3	**<0,001**	13,683	4,782	39,157
	T4	**<0,001**	9,824	3,324	29,031

PEROP: pre-operative diagnosis, PSOP: postoperative diagnosis CEA: carcinoembryogenic antigen (µg/L), CA19-9: cancer antigen 19-9 (kU/L), ALT: alanine aminotransferase (U/L), AST: aspartate aminotransferase (U/L), ALP: alkaline phosphatase (U/L), GGT: gamma glutamyl transferase (U/L), TBIL, DBIL: total/ direct bilirubin (mg/dL), CRP: C reactive protein (mg/L), ALB: albumin (g/L), CAR: CRP/ALB ratio, WBC: white blood cell (10^3/uL), HB: hemoglobin (g/L), PLT: platelet (10^3/uL), T: tumor size (TNM classification)

Table 6: Multivariate Cox Regression Analysis of Patients' Factors Determining Mortality

		p	HR	95% CI	
Time of diagnosis (Ref: PEROP) PSOP		0,685	0,787	0,248	2,496
CRP		**0,03**	0,963	0,93	0,996
ALB		0,215	1,775	0,716	4,402
CAR		**0,025**	1,12	1,015	1,237
Differentiation (Ref: Good differentiation)		0,005			
	Poor	**0,002**	7,292	2,019	26,34
	Middle	**0,003**	5,87	1,85	18,628

PEROP: pre-per operative diagnosis, PSOP: postoperative diagnosis, CRP: C reactive protein (mg/L), ALB: albumin (g/L), CAR: CRP/ALB ratio