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Prognostic value of the inflammatory markers derived from peripheral blood cell counts in gallbladder cancer

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Abstract: Objective: To study the potential predictors of patient survival, including the inflammatory markers derived from peripheral blood cell counts, in gallbladder cancer. **Patients and methods:** This study included patients diagnosed with gallbladder cancer and have follow up of at least 6 months. Patients who had cholangitis at diagnosis were excluded. The ratios of neutrophil to lymphocyte counts (NLR), platelet to lymphocyte counts (PLR), and monocyte to lymphocyte counts (MLR) were calculated at the time of diagnosis. **Results:** A total of 85 patients fulfilled the criteria and were involved in the analysis between July 2009 and January 2020. Thirty-five patients (41%) were females, and 50 (59%) were males. The mean age at the time of diagnosis with gallbladder cancer was 54 ± 12 years, and it ranged from 31 to 93 years. The mean follow-up period was 1.0 ± 0.7 years. Patient survival from the time of diagnosis until the last follow-up was 44.7%, with 47 patients died during the follow-up period; the median survival was 1.5 years. Cox's proportional hazard regression analyses were carried out and revealed that young age at diagnosis (HR=1.04, CI=1.01-1.07), PLR≤200 (HR=0.35, CI=0.17-0.70), and surgical resection (HR=0.10, CI=0.04-0.23) are associated with longer survival. **Conclusion:** Platelet/lymphocyte ratio can be a valuable and straightforward prognostic marker of gallbladder cancer.
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1. Introduction:

Gallbladder cancer (GBC) is a relatively uncommon cancer [1]. GBC is the most common among biliary tract cancers and has the worst prognosis [2]. Data from the Surveillance, Epidemiology and End Results program found the incidence of GBC is approximately 2.5 per 100,000 persons; and accounts for 46% of biliary tract cancers. Symptoms are usually unspecific, leading to a delayed presentation or presenting a picture similar to gallstone disease. As a result, it is usually picked up on histopathology for routine cholecystectomies [3]. Since the introduction of laparoscopy, diagnosis of GBC at an early stage has increased markedly [4]. The most important prognostic factor for Gallbladder cancer is the tumor stage [5]; yet, there still is no reliable markers identified for routine screening for early identification of Gallbladder cancer [6, 7]

Over the past few years, interest has taken place in the role of inflammatory markers and their prognostic value in various cancers [8]. To date, there have been many studies looking at the role of inflammatory markers as a prognostic indicatory in gallbladder cancer [9-15]. In addition, a clear tie has been demonstrated between the elevation of inflammatory markers, such as neutrophil to lymphocyte and platelet to lymphocyte ratios and decreased survival [9].

Given that complete R0 surgical resection is the only proven cure for gallbladder cancer, attempts must be made at finding better ways of picking up early lesions [16]. In addition, due to most cases being discovered incidentally upon cholecystectomy and even in suspected cases, the depth of invasion can only be identified upon final histopathology. There is a clear need for additional prognostic tools

that can aid in making clinical decisions [3]. In this study, we aimed to study further the relationship between the inflammatory markers derived from peripheral blood cell counts, including neutrophil to lymphocyte (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) and gallbladder cancer, and their ability to predict patient survival.

2. Methods:

Our study is a retrospective analysis of prospectively collected data undertaken at Hamad General Hospital, a tertiary hospital in Doha, Qatar. The period under review was between July 2009 and January 2020.

Using our database from the hepatobiliary multidisciplinary team meeting, 88 cases were identified with at least 6 months of follow up from diagnosis, for recently diagnosed alive patients. Patients who had cholangitis at the time of diagnosis were excluded.

In patients with suspected GBC, the diagnosis was made through biopsy and imaging. The staging was done using multi-detector computed tomography (MDCT) or magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG-PET). According to the American Joint Committee on Cancer (AJCC) staging system [17].

Patients were considered to have incidental GBC if malignancy was detected on histopathological examination without preoperative suspicion of GBC. The extent of the tumor was determined based on the pathological examination of the removed gallbladder, and proper staging was done using MDCT or MRI and FDG-PET to exclude metastatic disease.

Simple cholecystectomy alone was felt to be adequate for patients with tumors that are limited to the lamina propria (T1a), while patients with a GBC >T1a, completion hepatectomy was considered as shown below in detail.

Surgical procedures:

Patients, who were candidates for radical resection with proper radiological staging and no evidence of metastasis, underwent a diagnostic laparoscopy first. Completion hepatectomy included resection of segments IVb and V, excision of porta hepatis and supra-duodenal lymph nodes with or without bile duct resection, Roux-en-Y hepaticojejunostomy, depending on the cystic duct margin. Resection was classified as R0, R1 or R2 depending on the margin status (R0 = no residual disease, R1 = microscopically positive margin, and R2 = macroscopic residual disease).

Patient electronic files were accessed and double-checked using our Electronic Medical Viewer. Collected data included age, gender, ethnicity, laboratory results (blood cell count, liver and renal function tests, and tumor markers), American Society of Anesthesiologists Physical Status Classification (ASA) (18), clinical performance status (19), type of surgical intervention, lympho-vascular invasion, perineural invasion, stage, presence or absence of metastatic disease, and outcome.

The NLR was defined as the absolute neutrophil count in peripheral blood divided by the absolute lymphocyte count, PLR was defined as the platelet count divided by the absolute lymphocyte, and MLR was calculated as the absolute monocyte count divided by the absolute lymphocytic count. All ratios were calculated at the time of diagnosis. PLR of 200 was used as a cut off value [15].

The Ethical Committee approved our retrospective study for Human Research at our institute.

Statistical analysis:

Data were expressed as mean ± standard deviation and frequency (percentage). Survival curves were drawn using the Kaplan-Meier method and log-rank test for comparison. Cox's proportional hazards regression was used to identify the predictors of patient survival. Patients who are still alive or lost the follow up were considered censored.

A *P*-value of <0.05 was considered statistically significant. SPSS software (SPSS Inc., Chicago, USA, version 22) was used for analysis.

3. Results:

A total of 85 patients with gallbladder cancer met the criteria and were included in the analysis. Thirty-five patients (41%) were females, and 50 (59%) were males. The average age at the time of diagnosis was 54 ± 12 years, and it ranged from 31 to 93 years. The mean follow-up was 1.0 ± 0.7 years.

Forty-eight patients (56.5%) were Asian, mainly from India and Bangladesh, 33 (38.8%) were Middle Eastern, 3 patients (3.5%) were Africans, and 1 patient (1.2%) was European. Clinical performance was reported as status 0 for 59 patients, and 1 for 16 patients, while status 2, 3, and 4 were reported in 6, 2, and 2 patients, respectively.

TNM staging revealed that 2 patients had carcinoma-in-situ; 12 patients were stage 1, 20 patients were stage 2, and 7 patients were stage 3, while 44 patients were stage 4.

Pathological examination showed well-differentiated gallbladder carcinoma in 19 patients; 28 patients had moderately differentiated carcinoma, 23 had poorly differentiated carcinoma, and 7 had undifferentiated carcinoma.

A summary of patients' characteristics can be found in Table 1.

Table 1: Patient Characteristics

Characteristics	Value
Age (years)	54 ± 12
Gender	
Male	50 (59%)
Female	35 (41%)
Follow up (years)	1.0 ± 0.7
Ethnicity	
Asian (mainly India and Bangladesh)	48 (56.5)
Middle Eastern	33 (38.8)
African	3 (3.5)
European	1 (1.2)
ASA*	
1	11
2	36
3	20
4	9
Performance status	
0	59
1	16
2	6
3	2
4	2
Stage	
0 (In situ)	2 (2.4%)
I	12 (14.1%)
II	20 (23.5%)
III	7 (8.2%)
IV	44 (51.8%)
Differentiation	
Well-differentiated	19 (24.7)
Moderately differentiated	28 (36.3)
Poorly differentiated	23 (29.9)
Undifferentiated	7 (9.1)

*ASA: The American Society of Anesthesiologists physical status classification system

Surgical details:

A total of 43 patients underwent surgery, 22 patients (51.2%) had laparoscopic cholecystectomy for benign disease diagnosis. Based on the pathological findings, 4 out of 22 patients had carcinoma in situ or GBC stage 1A, and cholecystectomy alone was appropriate for them. In addition, 18 out of 22 patients required completion hepatectomy for resection of liver segments 4b and 5 in addition to lymphadenectomy. Only 8 patients underwent the planned resection, and 10 patients did not proceed due to poor general conditions or refused to travel back home.

12 patients (27.9%) underwent extended cholecystectomy including removal of the gallbladder en-bloc with resection of liver segments 4b and 5 in addition to lymphadenectomy, 5 out of these 12 patients had minimal invasive approach.

Four patients (9.3%) underwent central hepatectomy, including resection of liver segments 4 and 5 in addition to bile duct resection and biliary reconstruction with Roux-en-Y hepaticojejunostomy entero-enterostomy.

Three patients (6.9%) underwent an extended right hepatectomy with excision of the bile duct and biliary reconstruction with Roux-en-Y hepaticojejunostomy entero-enterostomy.

On diagnostic laparoscopy, two patients (4.7%) showed advanced disease with peritoneal and liver metastases, and surgery was aborted.

Predictors of survival in gallbladder cancer patients:

Patient survival from time of diagnosis until the last follow-up was 44.7%, with 47 patients died during the follow-up period; and the median survival was 1.5 years (Figure 1).

Cox's proportional hazard regression analyses were carried out in relation to patient survival at 3 years from diagnosis.

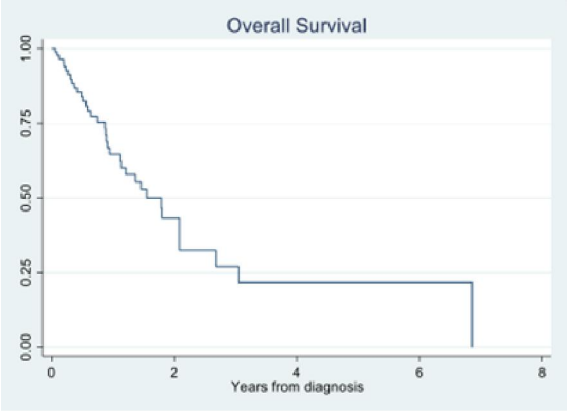

Figure 1: The overall patient survival from the time of diagnosis until the last follow up

Univariate analysis:

Univariate analysis revealed better survival for younger patients at time of diagnosis, PLR ≤200, early stage of the disease (stages 1 and 2), in addition to patients who underwent surgical resection with an intent-to-cure (Table 2).

Other inflammatory markers, including NLR and MLR in addition to the tumor markers CA 19-9 and CEA did not significantly impact patients' survival at 3 years. Race of patients, ASA, and clinical performance status was checked but did show a relation to survival.

Table 2: Predictors of patient survival after 3 years

Variables	Hazard ratio	95% Confidence Interval	*P*-value
Gender (male vs. female)	0.99	0.500– 1.974	0.986
Age	1.05	1.020 – 1.081	0.001
ASA			
1	1		
2	1.89	0.478 – 3.230	0.992
3	1.04	0.304 – 3.331	0.445
4	2.64	0.610 – 25.201	0.085
Early vs. late stage	2.64	1.411 – 4.483	<0.001
Tumor differentiation			
Well differentiated	1		
Moderately differentiated	0.93	0.374 – 2.401	0.871
Poorly differentiated	1.24	0.454 – 3.442	0.667
Undifferentiated	3.65	0.612 – 16.120	0.091
NLR	1.03	0.965 – 1.120	0.191
PLR	1.05	1.012 – 1.059	0.009
MLR	1.45	0.496 – 4.256	0.495
Surgical resection	0.10	0.038 - 0.225	<0.001

ASA, The American Society of Anesthesiologists physical status classification system; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; MLR, monocyte/lymphocyte ratio.

Multivariate analysis:

Factors identified during univariate analysis were examined together under multivariate analysis after adjusting for the stage of the disease, PLR cut-off value of 200 was used in the multivariate analysis to assess the potential hazard risk for practical application. Age at diagnosis (HR=1.04, CI=1.01-1.07), PLR≤200 (HR=0.35, CI=0.17-0.70), and surgical resection (HR=0.10, CI=0.04-0.23) (Figure 2), and surgical resection with an intent-to-cure (HR=0.10, CI=0.038-0.225) (Figure 3) were independent predictors of a better survival at 3 years (Table 3).

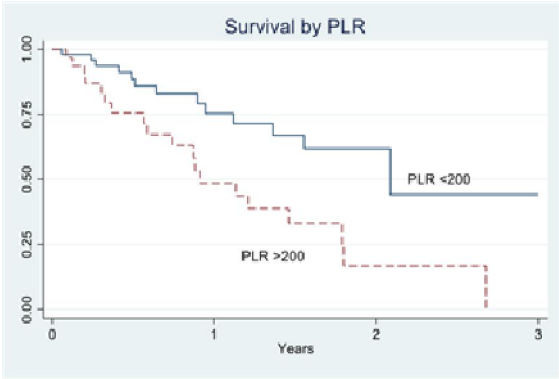

Figure 2: The survival analysis of patients with GBC. The Kaplan–Meier curve analysis shows higher survival rates at 3 years of follow up for the patients presenting with PLR≤200 compared to those with PLR>200

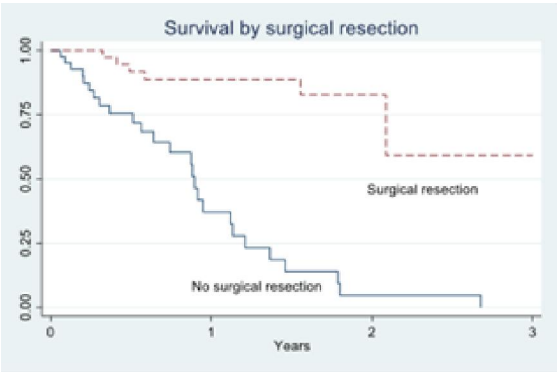

Figure 3: The survival analysis of patients with GBC. The Kaplan–Meier curve analysis shows higher survival rates at 3 years of follow up for the patients who underwent surgical resection with an intent-to-cure

Table 3: Multivariate analysis

Variables	Hazard Ratio	95% Confidence Interval	*P*-value
Age	1.04	1.01 – 1.07	0.003
Surgical resection (Yes vs. No)	4.30	1.52 – 13.4	0.008
Early vs. late stage	1.89	0.39 – 9.20	0.892
PLR (≤200 vs. >200)	2.86	1.92 – 5.96	0.024

4. Discussion:

Gallbladder cancer remains the most common biliary tract cancer with an incidence of 2.5 per 100,000 persons; and, generally, is the most aggressive and confers the worst prognosis [2]. With

an R0 surgical resection remaining as the most successful treatment modality, an attempt must be made to identify this pathology at earlier stages. However, to date, it is incidentally found in most patients who undergo cholecystectomy with a benign condition in mind [4]. Furthermore, with a lack of reliable markers identified for routine screening, many prognostic factors confer an increased relationship with malignancy, such as, large stones and multiple polyps [6, 20]. Therefore, attempts must be made to identify additional prognostic factors or identify a reliable screening marker.

Over the past decade, inflammatory markers have been extensively studied about their value in various solid tumors ranging from uterine cancer to pancreato-biliary malignancies [7]. The pathophysiology behind the relation is multifaceted and involves the systemic response to multiple factors, including Interleukins, tumor necrosis factors, and granulocyte colony-stimulating factors, which eventually leads to neutrophilia, thrombophilia and lymphopenia [21]. A second step occurs, wherein neutrophilia releases harmful cellular compounds resulting in surrounding tissue necrosis, facilitating the extension of the tumor cells. The related lymphopenia further promotes tumor cell growth by decreasing circulating NK cells [21]. More so over the prognostic value of an elevated NLR and PLR in gallbladder cancer has been demonstrated in multiple studies [11, 16, 22].

This study looked at the potential predictors of patient survival at 3 years from diagnosis, including the inflammatory markers derived from peripheral blood cell counts (NLR, PLR, and MLR). PLR $\leq$200 was associated with significantly longer survival. Various studies had used different values to attain significance; however, a cutoff value of 200 seemed most in line with most published studies [9, 12, 14]. In our study, PLR at diagnosis is a predictor of patient survival. These results agree with published studies [12, 15] concerning PLR; however, in the study by Beal et al. [15], no statistical significance was found pertaining to PLR. Similarly, in literature, it was found that an elevated NLR was associated with worse overall survival in samples drawn both prior to and after surgical resection [10, 15]. However, in our cohort, NLR does not impact patients' survival. MLR was found be closely associated with inflammation in cancer patients, hence it has been studied in relation to patients' outcomes (23). In our study, we did not find a relation between MLR and patients' survival.

In addition to the inflammatory markers, surgical resection with an intent-to-cure is strongly associated with better survival using the multivariate analysis, similar to published literature results [10, 12]. Patient age was an independent predictor of survival. The older the patient, the higher risk of mortality. The precise mechanism remains unclear, but it might be due impairment of the immune response with advancing age (24).

In our cohort, patients diagnosed with metastatic disease showed significantly higher NLR and PLR at diagnosis. These results come in concordance with a study by Zhang et al., who similarly found that elevated NLR was related to the presence of metastasis [12]. However, in their study, they failed to demonstrate a significant value of PLR in relation to metastasis, which contrasts our findings where an elevated PLR was significantly related to the presence of metastasis.

Given the findings and the established value of inflammatory markers across a multitude of cancers it is within reason to assume that an inflammatory response starts well before the clinical detection of malignancy. The presence of an early elevation of inflammatory markers may reflect the microenvironment of said tumor and be an indicator of tumor growth and extension.

In companionship with the lack of reliable biochemical markers and screening tools in detecting gallbladder cancer, we propose the value of PLR in patients presenting with biliary symptoms. It is a cheap and easily attainable value [6, 22] and improves risk stratification, facilitating better patient selection for decision making in surgical resection or aggressive chemotherapy in gallbladder cancer patients [25].

Limitations of this study come from the retrospective nature, and the lack of a control arm concerning the value of inflammatory markers in patients with benign biliary diseases. A prospective study is better equipped to ascertain better the prognostic value of screening PLR or its value as an indicator for prophylactic cholecystectomy.

In conclusion, platelet/lymphocyte ratio can be a valuable and straightforward prognostic marker of gallbladder cancer.

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