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Association between red cell distribution width and laboratory parameters in gallbladder cancer

Asociación entre la amplitud de distribución eritrocitaria y los parámetros de laboratorio en cáncer de vesícula biliar

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ABSTRACT

Introduction: Red cell distribution width is a parameter frequently increased in chronic inflammation, metabolic disorders, and different human cancers. However, the relationship between RDW and gallbladder cancer (GBC) has been poorly documented. **Objective:** To evaluate the association between RDW with different laboratory parameters (biomarkers) and evaluate the survival curve in patients with GBC. **Materials and methods:** This is a retrospective study with univariate and multivariate analyses. The cases were divided into two large groups according to RDW values, previously defined cutoff value; RDW ≤ 14.5% (n = 20) and RDW >14.5% (n= 15), to evaluate the association with laboratory parameters and clinicopathologic variables. The Kaplan-Meier method was used to estimate survival as a function of time. **Results:** The higher the stage of GBC patients, the greater the tendency to have higher RDW values (stage IV 14.86 ± 1.184 vs III 13.41 ± 2.189 vs II 12.80 ± 2.393; p=NS). No significant correlation was found between RDW values and clinicopathological data. A significant association was observed between an RDW value >14.5% and higher serum concentration of creatinine (p=0.01) and sodium (p=0.0069). The univariate analysis showed that those patients who had a high level of total bilirubin, aspartate aminotransferase, alkaline phosphatase and chlorine presented a lower GBC survival (p<0.05). Multivariate analysis showed that RDW was not an independent prognostic factor for GBC (p=0.079), as were direct bilirubin (p=0.013) and alkaline phosphatase in our cohort (p=0.012). **Conclusion:** There was no a significant correlation between the RDW level and the prognosis of patients with advanced GBC. Bilirubin and alkaline phosphatase proved to be predictive biomarkers of this disease.

Keywords: Gallbladder cancer, red cell distribution width, biomarkers, survival.

RESUMEN

Introducción: La amplitud de distribución eritrocitaria (ADE) es un parámetro que se eleva frecuentemente en la inflamación crónica, trastornos del metabólismo y distintos cánceres humanos. Sin embargo, la relación entre ADE y el cáncer de vesícula biliar (CVB) no ha sido bien estudiada. **Objetivo:** Evaluar la asociación entre ADE con diferentes parámetros de laboratorio (biomarcadores) y evaluar la curva de supervivencia en pacientes con CVB. **Materiales y métodos:** Estudio retrospectivo con análisis univariado y multivariado. Los casos se dividieron en dos grupos según los valores de RDW, previamente definido; RDW ≤ 14,5 (n = 20) y RDW >14,5% (n= 15), para evaluar la asociación con parámetros de laboratorio y variables clínico-patológicas. Se utilizó el método de Kaplan-Meier para estimar la supervivencia en función del tiempo. **Resultados:** Cuanto mayor es el estadio de los pacientes, mayor es la tendencia a ADE elevado (estadio IV 14,86 ± 1,184 vs III 13,41 ± 2,189 vs II 12,80 ± 2,393; p=NS). No se encontró correlación significativa entre los valores de ADE y los datos clínico-patológicos. Se observó una asociación significativa entre un valor de ADE >14,5% y una mayor concentración sérica de creatinina (p=0,01) y sodio (p=0,0069). El análisis univariado mostró que aquellos pacientes que tenían un nivel alto de bilirrubina total, aspartato aminotransferasa, fosfatasa alcalina y cloro, presentaron una menor supervivencia (p<0,05). El análisis multivariado mostró que el ADE no fue un factor pronóstico independiente para el CVB (p=0,079) y si lo fue bilirrubina directa (p=0,013) y fosfatasa alcalina (p=0,012). **Conclusión:** No hubo una correlación significativa entre el nivel de RDW y el pronóstico de los pacientes con GBC avanzado. La bilirrubina y la fosfatasa alcalina resultaron ser biomarcadores predictivos de esta enfermedad.

Palabras Clave: Cáncer de vesícula biliar, amplitud de distribución eritrocitaria, sobrevida.

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INTRODUCTION

Gallbladder cancer (GBC) is a highly aggressive neoplasm of the biliary tract[1] and shows a marked geographical variation in incidence[2]. For instance, in Chile, this malignancy has become one of the leading causes of cancer-related deaths in women[3]. Despite advances in diagnosis and follow-up strategies, GBC continues to be a neoplasm with a poor prognosis[4], with an overall median survival of only six months, while the 5-year survival rate is less than 5% in advanced stages[5].

Therefore, new biomarkers for GBC - easy and accessible to analyze- are still needed to determine the prognosis and make the monitoring of the risk population. Red cell distribution width (RDW) is a qualitative parameter

routinely included in the complete blood count, whose value reflects the degree of variability in the size of circulating erythrocytes[6]. For this reason, RDW has basically been used in the differential diagnosis of deficiency anemias, together with other erythrocyte indices of the hemogram[7]. RDW describes the percentual variation of erythrocyte size, and is calculated in the following manner: (Erythrocyte volume standard deviation/Medium corpuscular volume) x 100.[8]

RDW values are influenced by different factors, such as chronic inflammation, and/or deficit in erythrocyte production due to iron metabolism alterations or abnormal erythropoietin levels, which are the main determinants of the RDW values[7]. In addition, RDW value alterations have been also associated with various disorders such as, hepatic diseases, ulcerative colitis, diabetes mellitus, and other abnormalities related to cardiovascular and renal systems[7], as well as several cancer types as for example breast and colorectal cancer.[9,10]

This association would be the consequence of a chronic inflammatory state produced during malignant processes, which could induce a harmful effect on DNA, triggering the malignant transformation of circulating cells. In cancer, the pro-inflammatory activity in pre-neoplastic states could cause the destabilization of the erythrocyte membrane and an alteration in its maturation process, generating a variation in the volume of these cells.[11]

There is scarce evidence that relates RDW with the biliary tract micro-environment during carcinogenesis[12]. The aim of this study was, therefore, to assess the association between RDW values and GBC stages, along with its relationship with other routinely used biochemical and hematological laboratory parameters and evaluate the survival curve of these patients.

MATERIAL AND METHODS

Research design

This is a non-experimental and retrospective study with univariate and multivariate analyses, which did not include the manipulation of biological material. Clinical history and laboratory parameters were obtained from the Clinical Laboratory database of the Hernán Henríquez Aravena Hospital, from Temuco.

This study included 35 GBC patients without previous treatment. For staging, we used the TNM system, grouping them in stages II, III, and IV.

We excluded all GBC patients who received any type of treatment prior to obtaining the results and those patients who had a hemoglobin concentration lower than 10 gr/dL, or other hematological disorders, such as anemias of deficiency or hemolytic type that could modify the RDW values.

This project was approved by the Research Ethics Committee of the Universidad Católica de Temuco, according to the Declaration of Helsinki.

Biochemical and hematological analysis

For this study, routine laboratory markers (hematological and biochemical parameters) will be used, which are normally used to evaluate the general condition of cancer patients. Analysis was performed at the time of diagnosis by Clinical Laboratory's qualified personnel. Hematological parameters such as count of red blood cells, white blood cells, platelets, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and RDW were assessed using the ADVIA 120 hematology analysis system (Siemens Healthineers, Washington, USA), which performs flow cytometry testing.[13]

For biochemical parameters such as serum concentration of total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase (ALP), glucose, creatinine, urea nitrogen, amylase, lipase, and plasma electrolytes sodium, potassium, and chloride, were analyzed using the chemiluminescence-based system ARCHITEC i2000 (Abbott Diagnostics, Abbott Park, USA).

Statistical analysis: The STATA v.14 software was used to perform statistical analysis. Each quantitative variable was figured in contingency tables. Shapiro-Wilk normality analysis was performed to categorize parametric and non-parametric variables.

Associations between RDW expression and relevant clinicopathologic features were analyzed using the Fisher exact test or Chi-squared test, as appropriate. To determine the differences between RDW values and biochemical and hematological parameters, a non-parametric test was used (Mann-Whitney) as appropriate and T student test to compare two groups with normal distribution. To compare the RDW values by TNM stage, (numerical variables) we have used the ANOVA test. Log-rank test and Kaplan-Meier curves were used to analyze the survival among the different groups. Multivariate analysis was performed using the COX regression model. Statistical significance was established with a p-value <0.05.

RESULTS

Table 1 shows the clinical and laboratory characteristics of GBC patients. The greater frequency of GBC patients was in stage III (43%), and were predominantly women (82.86% women vs 17.14% men). The age range was 48-90 years, with a mean of 68 years old. Regarding ethnicity, 31.4% of GBC patients belonged to the Mapuche ethnicity, according to the last name registry in the database.

On the other hand, to study the association of RDW with clinicopathological parameters, our cohort was divided into two large groups according to RDW values, which corresponds to the value (upper limit) that is normally used in clinical laboratories, both for men and women: RDW ≤ 14.5% (n=20) and RDW >14.5% (n=15).

In addition, GBC was stratified according to TNM stages. No significant association was found between RDW values and clinical parameters (gender, ethnicity, age, TNM stage) (Table 2).

Table 1. Clinical and laboratory characteristics of the study population (n=35)

Characteristics	Value
Female gender	29 (82.8%)
Male gender	6 (17.1%)
Mapuche ethnicity (%)	11 (31%)
Age range	48 - 90
Mean age ± SD	68 ± 11
Stage II	12 (34%)
Stage III	15 (43%)
Stage IV	8 (23%)
RDW (%)	13.53 ± 2.174
Erythrocytes (x106x mm3)	4.040 ± 0.4888
Leukocytes (x103x mm3)	12.20 ± 5.924
Platelets (x103x mm3)	308.7 ± 95.67
Hematocrit (%)	35.16 ± 4.205
Hemoglobin (g/dL)	11.83 ± 1.435
Mean Corpuscular Volume (fL)	86.71 ± 3.562
Mean Corpuscular Volume (pg)	29.29 ± 1.493
Glucose (mg/dL)	124.6 ± 60.59
Total Bilirrubin (mg/dL)	6.158 ± 8.451
Direct Bilirrubin (mg/dL)	5.193 ± 7.274
Aspartate aminotransferase (U/L)	71.13 ± 71.00
Alanine aminotransferase (U/L)	81.00 ± 110.0
Alkaline Phosphatase (U/L)	339.1 ± 282.9
Amylase (U/L)	52.63 ± 23.58
Creatinine (mg/dL)	0.7197 ± 0.2739
BUN (*blood urea nitrogen)*	13.79 ± 6.600
Sodium (mmol/L)	136.5 ± 3.596
Potassium (mmol/L)	3.664 ± 0.5482
Chlorine (mmol/L)	104.5 ± 5.361

Table 2. Association between RDW values and clinical parameters**.**

Variables	RDW ≤14.5%	RDW >14.5%	p
Women	18 (51.4%)	11 (31.4%)	0.367*
Men	2 (5.7%)	4 (11.4%)	
Ethnicity			
Mapuche	7 (20%)	4 (11.4%)	0.721*
Non-mapuche	13 (37.1%)	11 (31.4%)	
Age (years)			
< 65	6 (17.1%)	8 (22.8%)	0.18*
> 65	14 (40%)	7 (20%)	
Stage (TNM)			
II	7 (20%)	5 (14.2%)	
III	10 (28.5%)	5 (14.2%)	0.4 †
IV	3 (8.5%)	5 (14.2%)	
II – III	17 (62.9%)	10 (37%)	1.0 *
II – IV	10 (50%)	10 (50%)	0.11*
III – IV	13 (56.5%)	10 (43.4%)	0.37 *
II – III + IV	20 (57.1%)	15 (42.8%)	0.6 *

Statistical tests: * Fisher's exact test; † Chi-squared test; RDW, Red Cell tribution Width; TNM, Tumor-Node-Metastasis Staging. The percentages were calculated (n = 35)

When determining the comparison between RDW values and biochemical parameters, a statistically significant association was observed between RDW >14.5% and serum concentration of creatinine (p=0.01) and sodium (p=0.0069) (Table 3).

Table 3. Comparison between RDW values and biochemical and hematological parameters.

Parameters	RDW <14.5 (%)	n	RDW >14.5 (%)	n	p
Erythrocytes ($x10^6$x mm^3)	3.98 (3.1-4.8)	20	3.95 (3.6-5.38)	15	0.43*
Leukocytes ($x10^3$x mm^3)	10.9 (5.1-28.7)	20	10.0 (5.6-24.4)	15	0.49*
Platelets ($x10^3$x mm^3)	281.5 (156-492)	20	289 (191-572)	15	0.9*
Hematocrit (%)	35 (29.4-43.3)	20	35 (28.8-46.6)	15	0.8†
Hemoglobin (g/dL)	11.5 (10.1-15.4)	20	11.4 (10.3-15.2)	15	0.95*
Mean Corpuscular Volume (fL)	87.2 (86.6-96.5)	20	86 (80.1-90.2)	15	0.55†
Mean Corpuscular Hemoglobin (pg)	29.5 (26-32.1)	20	28.9 (27-30.3)	15	0.23†
Glucose (mg/dL)	109 (81-316)	14	104.5 (75-139)	10	0.24*
Total Bilirubin (mg/dL)	4.8 (0.2-32.8)	17	1.2 (0.3-21.6)	14	0.53*
Direct Bilirubin (mg/dL)	4.4 (0.1-25.8)	15	1.1 (0.2-16.4)	13	0.53*
Aspartate aminotransferase (U/L)	59.5 (14-316)	18	28 (13-154)	13	0.69*
Alanine aminotransferase (U/L)	62 (13-543)	18	27 (11-371)	13	0.62*
Alkaline Phosphatase (U/L)	396 (85-1201)	17	241(69-598)	10	0.17†
Amylase (U/L)	49 (20-94)	14	58 (22-118)	10	0.34†
Creatinine (mg/dL)	0.6 (0.1-1.1)	15	0.85 (0.6-1.2)	14	0.01†
BUN	13 (7-27)	12	14 (6-36)	12	0.86*
Sodium (mmol/L)	135.5 (129-139)	12	139 (131-142)	10	0.0069*
Potassium (mmol/L)	3.6 (3-5.2)	12	3.75 (3-4.4)	10	0.5†
Chlorine (mmol/L)	103 (93-108)	12	106.7 (104-118)	10	0.085†

BUN (*blood urea nitrogen);* Statistical tests: *Mann- Whitney; † T-Student test.

According to data distribution by stage of the disease, it was observed GBC patients slightly increase their RDW values as the TNM stage also increase: II (12.80 ± 2.393) vs III (13.41 ± 2.189) vs IV (14.86 ± 1.184). The statistical analysis

(ANOVA test) provides a p value of 0.1088. This variability and distribution of the data are observed in Figure 1.

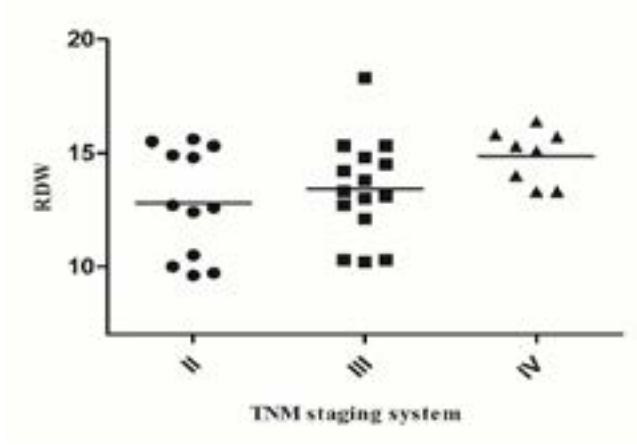

Figure 1. Frequency distribution of RDW values according to GBC TNM stage.

The survival analysis considered the patient´s follow-up from the time of diagnosis until death. The Kaplan-Meier graph shows that both patient groups presented a sharp drop in the survival curve within the first month of follow-up. Then, curves moved apart and a slightly lower survival was observed in the group with RDW <14.5% from month 8 (p = 0.116) (Figure 2). The entire cohort (n=35) had an estimated survival of 14.2% with a median survival of 7.3 months.

Survival curves represented as a solid line for patients with RDW ≤14.5% and as a dashed line for patients with RDW >14.5%. No statistically significant differences are observed.

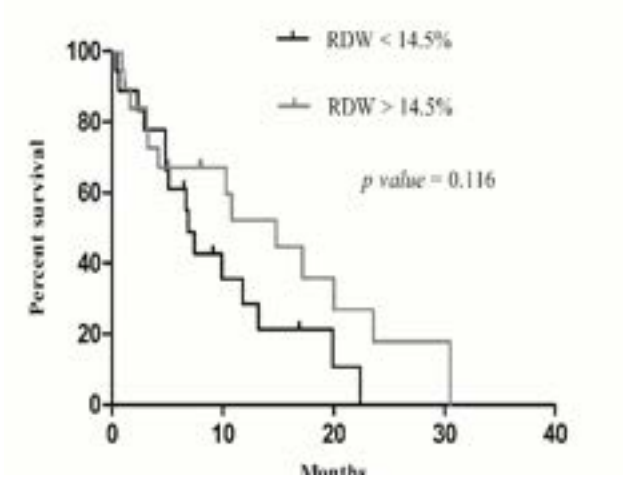

Figure 2. Kaplan-Meier survival analysis for 35 GBC patients, stratified by RDW value.

In the univariate analysis, patients who had high levels of total bilirubin, aspartate aminotransferase, ALP and chlorine, showed a lower GBC survival (P<0.05; Table 4). On the other hand, the multivariate analysis showed that RDW was not an independent prognostic factor for GBC (P=0.079; Table 4); however, high serum levels of direct bilirubin and ALP effectively showed to be independent prognostic factors for GBC (p = 0.013 and 0.012 respectively; Table 4).

Table 4. Univariate and multivariate analysis, hazard ratio model for survival (n=35).

Variables	Univariate analysis		CI (95%)	Multivariate analysis		CI (95%)
	HR	p *		HR	p *	
RDW>14.5%	0.50	0.075	0.2-1.0	0.51	0.079	0.24-1.0
Leukocytes	0.71	0.35	0.35-1.4	0.76	0.46	0.37-1.5
Erythrocytes	0.62	0.2	0.29-1.3	0.59	0.18	0.27-1.2
Platelets	1.7	0.3	0.59-5.3	1.6	0.3	0.55-5.0
Hemoglobin	0.54	0.14	0.24-1.24	0.49	0.1	0.21-1.1
Hematocrit	0.79	0.53	0.39-1.6	0.67	0.29	0.3-1.4
Mean Corpuscular Hemoglobin	0.76	0.56	0.3-1.9	0.83	0.71	0.3-2.1
Total bilirubin	2.68	0.013	1.2-5.8	2.68	0.013	1.2-5.8
Direct bilirubin	2.01	0.12	0.82-4.8	2.2	0.075	0.9-5.6
Aspartate aminotransferase	2.37	0.032	1.07-5.25	2.01	0.1	0.8-4.7
Alanine aminotransferase	1.77	0.13	0.83-3.7	1.39	0.44	0.59-3.2
Alkaline phosphatase	3.85	0.010	1.37-10.8	3.81	0.012	1.43-10.7
Glucose	0.91	0.84	0.38-2.1	1.07	0.87	0.4-2.5
Creatinine	0.9	0.87	0.2-3.0	1	0.99	0.29-3.4
BUN	0.95	0.94	0.2-4.1	1.07	0.92	0.24-4.7
Chlorine	0.3	0.047	0.12-0.98	1.0	0.99	0.42-2.3
Sodium	0.9	0.96	0.38-2.4	0.87	0.82	0.24-3.0
Potassium	1.1	0.72	0.48-2.8	1.16	0.7	0.47-2.8

*Cox regression. Abbreviation: HR, Hazard Ratio; CI, Confidence interval.

DISCUSSION

The RDW value is affected by various factors such as erythropoietin levels, increased oxidative stress, and iron metabolism disorders[7]. In addition, RDW values are strongly influenced by the chronic inflammation state observed in cancer patients, which is induced by both genetic and epigenetic alterations in oncogenes and/or tumor suppressor genes[14]. In this study, we observed an estimated survival of 14.2% with a median survival of 7.3 months.

These results are consistent with those described by Vijayakumar et al.[5] who observed a median survival of 6 months and a 5-year survival lower than 5% in advanced stages. In this regard, GBC cases were more frequent in elderly female patients. In addition, no significant association was found between RDW values and some clinical parameters (gender, ethnicity, age, TNM stage).

Statistically significant differences were found between RDW values and serum concentration of creatinine (p= 0.01) and

sodium (p= 0.0069). Serum creatinine levels, together with the serum concentration of other nitrogenous analytes such as uric acid and urea, are used as first-line tests to evaluate renal function.[15]

Meanwhile, sodium is the most abundant extracellular cation in the body, whose primary functions are to maintain plasma osmolarity and regulate cell membrane potential. Measurements of serum sodium concentrations are part of the second-line laboratory tests to evaluate renal function, mainly because the kidney is responsible for regulating both circulating volume and osmolarity of plasma through the processes of reabsorption, secretion, and excretion[16,17].

Although both parameters (creatinine and sodium) were within the reference values, we cannot rule out any incipient kidney damage, which must be evaluated with other studies such as urinary sediment, glomerular filtration rate, microalbuminuria, proteinuria, among others, and complementary tests (radiological examinations). If there is any degree of nephropathy, this could alter the synthesis of the hormone erythropoietin, which is produced in the kidney and is essential for the erythrocytes maturation in bone marrow, becoming one of the main determinants of RDW fluctuations[7,18]. These results may also have been influenced by the ethnic differences of the study population, the 31% of the subjects correspond to the Mapuche ethnic group and, according to the evidence, Latin American populations are the result of a mix of Caucasian, Amerindian, and Negroid populations. Recent studies have shown that the Chilean population has 42% Amerindian ancestry.[19]

Our study showed no significant association between RDW values and GBC survival, however, a trend of worse prognosis was observed in patients with an RDW < 14.5%, which is very similar to that reported by Li et al.[20], who observed a significant relationship of RWD standard deviation > 40.2 and RDW coefficient of variation > 12.6 with a better survival of patients with intrahepatic cholangiocarcinoma, suggesting that, as well as in our study, elderly patients with possibly undetected anemia and malnutrition can lead to high RDW values, which reduces the importance of the prognostic role of this parameter in individuals[20]. On the contrary, patients with hilar cholangiocarcinoma (after surgery) with RDW > 14.95 had a significantly worse 5-year OS than patients with RDW < 14.95 (12.0% vs. 38.7%, p < 0.001).[21]

Studies in other cancers have shown dissimilar results regarding the usefulness of RDW as a marker of survival or as a marker for differential diagnosis. For example, Koma et al.[22] found that high RDW values were associated with a poor prognosis in lung cancer (p=0.002). Another study showed that the prognosis of gastric cancer patients can be accurately predicted by using RDW[23]. In addition, the combination of RDW, mean platelet volume and CA125, improved the differential diagnosis between endometrial cancer and endometrial hyperplasia[24]. On the contrary, Kos et al.[25] found no significant association between RDW values and survival for lung cancer patients (p=0,083). Similar results were obtained by Xu et al.[26] in a meta-analysis, which indicated that RDW was not associated with poor prognosis in esophageal cancer patients.

Gupta et al.[27] found that Stage IVB, there were more patients with high RDW (78%) than normal RDW (21.8%). However, the results were not statistically significant (p< 0.073). In stage IV high RDW predicted more tumour burden[27]. In a retrospective study conducted on the Chinese population, the RDW values showed a significant correlation with the TNM stage, which could suggest that RDW constitutes a risk factor for metastasis in GBC[28]. Conversely, another recent study, using a large number of patients, found that RDW could not predict recurrence nor survival in patients with potentially resectable GBC; however, in those cases including stage II and III, a lower value of RDW was associated with better prognosis.[29]

In this study, certain parameters such as total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) and chlorine, showed a significant association with lower GBC survival. Moreover, direct bilirubin and alkaline phosphatase were demonstrated to be independent prognosis predictors for GBC in our population. Previous studies had related total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and the tumor marker CA-125, as prognostic factors for GBC1[2,30]. Bilirubin, AST and alkaline phosphatase are well-known tests that are routinely used to evaluate liver function. Bilirubin is the main bile pigment and is produced by the degradation of the heme group from hemoglobin after the destruction of old or defective erythrocytes in the spleen[31]. In chronic liver diseases, pathologic elevation of conjugated bilirubin is predominant, and direct and total bilirubin levels usually rise together[32]. In GCB, it has been reported that the patients may present preoperative jaundice (generally due to infiltration of the extrahepatic bile duct by cancer), being a marker of advanced disease and poor prognosis.

Studies have shown that, the patients with GBC may present preoperative jaundice (generally due to infiltration of the extrahepatic bile duct by cancer), being a marker of advanced disease and poor prognosis[33]. Meanwhile, AST is released into the bloodstream when occurring some damage at hepatocellular level[34], we observed in this study that AST presented an HR of 2.37 (Table 4), which is positively associated with the event probability and, thus, negatively associated with the length of survival.

On the other hand, alkaline phosphatase is present especially in bone cells, hepatocytes and biliary epithelium, so its elevation in serum is not specific of hepatobiliary pathologies. At the liver level, alkaline phosphatase, along

with gamma-glutamyl transpeptidase, are usually elevated in serum when occurring bile duct obstructions[35]; alkaline phosphatase presented an HR of 3.85 (Table 4).

Interestingly, previous studies have shown that total bilirubin and alkaline phosphatase are helpful to differentiate between a benign and malignant biliary obstruction[12]. Interestingly, the study of Goussous et al.[36] found that the patients with Incidental GBC had significantly higher values for white blood cell count, glucose, alanine aminotransferase, prothrombin time, alkaline phosphatase (216.67 U/L vs. 109.47 U/L), total bilirubin level (3.74 mg/dl vs 0,94) and direct bilirubin 1,28 vs 0,35 mg/dL, p value < 0.00136.

In the same way Pitt et al.[37] and Stepien et al.[38], observed that alkaline phosphatase levels were significantly associated with the development of gallbladder and the biliary tract cancer risk. Alkaline phosphatase is produced in the membranes of cells lining bile ducts and appears elevated in extrahepatic disease. The positive association of alkaline phosphatase with GBTC risk may be due to chronic inflammation in the bile ducts, which then affects liver function.[38]

Some of the limitations of our study, are associated with the sample size, which restricts our analysis capacity, and with the use of observational data analysis which does not allow us to distinguish causality from the association. In addition, the differences found between our study and other studies could be related to the selected population, the inclusion and exclusion criteria, statistical methods applied in analysis, and the RDW cut-off values. However, the results of this study associate others routinely use and easily accessible laboratory parameters with the GBC.

In conclusion, our study found no significant correlation between the RDW level and the prognosis of patients with advanced GBC. A trend of a slightly lower survival was observed from month 8 in patients with an RDW < 14.5%. Additionally, the biochemical parameters (total bilirubin and alkaline phosphatase) proved to be useful as a prognostic factor, which could be related to the degree of metastases to other organs.

These biomarkers are mainly used as indicators of liver disease, there being little information on their prospective association with risk and prognosis in GBC, so we believe that this information contributes significantly to the area of clinical oncology in a cancer with a high incidence. However, the validation of these results in a larger cohort of patients is proposed.

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