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Research Article

THE ROLE OF C-REACTIVE PROTEIN AND ALBUMIN COMBINED INDEXES IN ACUTE CHOLECYSTITIS

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Abstract: *This study aimed to determine and compare the abilities of the C- reactive protein to albumin ratio, Glasgow prognostic score, and modified-Glasgow prognostic score to predict short-term mortality in patients with acute cholecystitis. This retrospective study used the examinations and data of patients who attended the Emergency Department were used. This study included patients aged ≥18 years with radiologically-, clinically-, and laboratory-confirmed acute cholecystitis diagnoses and hemogram and biochemical parameters measured and registered by the Emergency Department. This study included 269 patients aged 58.3±17.4 years, of which 51% were women. The abilities of C-reactive protein to albumin ratio, Glasgow prognostic score, and modified-Glasgow prognostic score to predict mortality were found to be statistically significant. Their AUC values were 0.73 (0.09–0.98) for C- reactive protein to albumin ratio, with a cut-off value of 3.9 (p = 0.003), 0.72 (0.10–0.97) for Glasgow prognostic score with a cut-off value of 2 (p = 0.006), and 0.73 (0.10–0.97) for the modified-Glasgow prognostic score with a cut-off value of 2. Inflammatory markers, including C- reactive protein and albumin, can predict the expression prognosis of patients with acute cholecystitis, as in many other diseases.*

Keywords: *C- reactive protein, albumin, C- reactive protein to albumin ratio, Glasgow prognostic score, modified-Glasgow prognostic score*

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1. Introduction

Acute cholecystitis is an inflammatory disease of the gallbladder that develops within hours. In most cases, the underlying etiology is cystic duct obstruction due to an embedded stone in the gallbladder neck or cystic duct. Early diagnosis and treatment significantly decrease morbidity and mortality [1,2]. It requires constant monitoring for ongoing inflammation. Diagnosis is based on liver function tests, leukocyte levels, and C-reactive protein (CRP) values [3]. Albumin and CRP are acute-phase proteins. In addition to being an inflammation marker, albumin provides information about the nutritional status [4].

Studies have shown that the CRP to albumin ratio (CAR) reflects the general nutritional status of the patients and systemic inflammation [4-8]. CAR has been studied in patients with malignancies [4,5],

Crohn's disease [6], sepsis [7], pneumonia [8], and coronavirus disease 2019 (COVID-19) [9]. In addition, recent studies on patients with inflammatory diseases [10-12] and acute cholecystitis [13-15] suggest that the CAR, Glasgow prognostic score (GPS), and modified GPS (mGPS) are effective in evaluating acute cholecystitis prognosis in patients. It has also been reported that GPS and mGPS are effective in predicting prognosis in colorectal cancers [16,17].

GPS and mGPS are calculated using CRP and albumin values. The GPS criteria were as follows: 0 points, CRP ≥10 mg/L and albumin ≥35 g/L; 1 point, CRP ≥10 mg/L or albumin <35 g/L; 2 points, CRP >10 mg/L and albumin is <35 g/L. The mGPS criteria were as follows: 0 points, CRP ≤10 mg/L and albumin ≥35 g/L; 1 point, CRP >10 mg/L; 2 points, CRP >10 mg/L and albumin <35 g/L(13-15). GPS and mGPS are thought to reflect systemic inflammation [16,17].

This study aimed to determine and compare the abilities of the CAR, GPS, and mGPS to predict short-term mortality in patients with acute cholecystitis.

2. Materials and Methods

2.1. Ethics

This study was approved by the Ethics Committee of the University of Health Sciences and Ümraniye Education and Research Hospital (Date: 29/09/2022, Decision No: B.l0.1.TKH.4.34.H.GP.0.01/302).

2.2. Study Design

Acute cholecystitis patients aged ≥18 who attended the Ümraniye Education and Research Hospital's Emergency Department between January 1, 2019, and June 1, 2022, were included in this retrospective study.

2.3. Study Population

This study included patients aged ≥18 years with radiologically-, clinically-, and laboratory-confirmed acute cholecystitis diagnoses and hemogram and biochemical parameters measured and registered by the Emergency Department. All patients aged <18 years or with additional trauma history or missing data were excluded from this study.

2.4. Data Collection

This retrospective study used the examinations and data of patients who attended the Emergency Department were used. These data included: demographic characteristics, background information (hypertension, malignancy, diabetes mellitus, hypothyroidism, coronary artery disease, chronic obstructive pulmonary disease, heart failure, chronic renal failure), laboratory test results (hemoglobin, hematocrit, white blood cell [WBC], lymphocyte, neutrophil, monocytes, basophil, mean corpuscular volume, red blood cell distribution width [RDW], platelets, mean platelet volume, creatinine, aspartate aminotransferase, alanine aminotransferase, CRP, and albumin values), CAR, GPS, mGPS, and hospital stay length. Ancillary radiological examinations were mostly ultrasound; it was rarely diagnosed with computerized tomography. The patients were divided into two groups—survivors and non-survivors—based on their status in Turkey's National Death Notification System. Hospital stay length and intensive care unit admission rates were recorded using the hospital's data system.

2.5. GPS

The GPS criteria were as follows: 0 points, CRP ≥10 mg/L and albumin ≥35 g/L; 1 point, CRP ≥10 mg/L or albumin <35 g/L; 2 points, CRP >10 mg/L and albumin is <35 g/L.

2.6. Modified GPS

The mGPS criteria were as follows: 0 points, CRP ≤10 mg/L and albumin ≥35 g/L; 1 point, CRP >10 mg/L; 2 points, CRP >10 mg/L and albumin <35 g/L.

2.7. Statistical Analysis

The Statistical Package for Social Sciences (SPSS) software (v.20; Chicago, IL, USA) was used for all statistical analyses. The normality of continuous data was assessed using the Shapiro–Wilk test. Continuous variables are presented as median (range), categorical variables as number (percentage), and quantitative variables as median (interquartile range; 25th-75th percentile). Categorical data were compared using Fisher's exact and Chi-square tests. Continuous data were compared pairwise using Mann–Whitney tests. This analysis calculated the area under the receiver operating characteristic curve (AUC) for parameters, tested them for mutual significance with the DeLong quality test and assessed their accuracy, specificity, sensitivity, and 95% confidence interval data. All results with $p < 0.05$ were considered statistically significant.

3. Results

This study included 269 patients aged 58.3±17.4 years, of which 51% were women. Age was significantly positively correlated with mortality ($p < 0.001$). In addition, hospital stay length was significantly longer in non-surviving than surviving patients ($p < 0.001$). Moreover, a coronary artery disease history was significantly more common in non-surviving than surviving patients ($p < 0.001$). The relationships between demographic characteristics and comorbid diseases and mortality are shown in Table.1.

Table 1. Relationship between demographic characteristics, comorbidities, and mortality

	Survivor (n=259)	Non-survivor(n=10)	Total (n=269)	p-value
Age				
Mean ± SD	57.6 ± 17.2	77.5 ± 12.4	58.3 ± 17.4	< 0.001
Range	19.0-90.0	54.0-96.0	19.0-96.0	
Sex				
Male	127.0 (49.0%)	3.0 (30.0%)	130.0 (48.3%)	0.2372
Female	132.0 (51.0%)	7.0 (70.0%)	139.0 (51.7%)	
LOS (day)				
Mean ± SD	5.3 ± 3.7	14.4 ± 14.9	5.7 ± 4.9	< 0.001
Range	1.0-31.0	2.0-37.0	1.0-37.0	
Comorbidities				
Hypertension	117.0 (45.2%)	7.0 (70.0%)	124.0 (46.1%)	0.1222
Diabetes mellitus	63.0 (24.3%)	2.0 (20.0%)	65.0 (24.2%)	0.7542
Malignancy	10.0 (3.9%)	0.0 (0.0%)	10.0 (3.7%)	0.5272
Hypothyroidism	6.0 (2.3%)	0.0 (0.0%)	6.0 (2.2%)	0.6262
Chronic obstructive pulmonary disease	18.0 (6.9%)	2.0 (20.0%)	20.0 (7.4%)	0.1232
Coronary artery disease	40.0 (15.4%)	6.0 (60.0%)	46.0 (17.1%)	< 0.001
Heart failure	16.0 (6.2%)	3.0 (30.0%)	19.0 (7.1%)	0.0042
Chronic renal failure	14.0 (5.4%)	0.0 (0.0%)	14.0 (5.2%)	0.4502

(LOS: length of hospital stay)

Mortality was significantly correlated with the laboratory test parameters for neutrophils ($p = 0.035$), monocytes ($p = 0.031$), and lymphocytes ($p = 0.017$). In addition, hemoglobin and hematocrit were negatively correlated with RDW and mortality ($p = 0.001$, $p = 0.001$, $p = 0.002$, respectively). Moreover, mortality was negatively correlated with albumin levels ($p = 0.024$) but positively correlated

with CRP levels (p = 0.042). Furthermore, CAR, GPS, and mGPS were significantly higher in non-surviving than surviving patients (p = 0.012, p = 0.006, and p = 0.006, respectively). The relationships between mortality and laboratory test parameters, CAR, GPS, and mGPS are shown in Table 2.

Table 2. Relationship of laboratory tests, CAR, GPS, and MODFGPS with mortality

Characteristic		Survivor	Non-survivor	Total	p-value
WBC	(10^3µ/L)	12.8 (10.0-17.0)	18.6 (10.9- 25.0)	12.8 (10.0- 17.2)	0.077
Neutrophil	(10^3µ/L)	10.2 (7.3-14.1)	17.2 (8.7- 22.7)	10.3 (7.3-14.4)	0.035
Monocyte	(10^3µ/L)	0.7 (0.5-1.0)	1.0 (0.8-1.2)	0.7 (0.5-1.0)	0.031
Lymphocyte	(10^3µ/L)	1.6 (1.1-2.2)	0.9 (0.7-1.6)	1.6 (1.1-2.2)	0.017
Basophil	(10^3µ/L)	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.906
Hemoglobin	(g/dl)	13.3 (11.9-14.6)	11.1 (9.6-12.1)	13.2 (11.8-14.6)	0.001
Hematocrit	(%)	40.2 (36.7-44.1)	33.0 (29.2- 36.9)	39.9 (36.5-44.0)	0.001
MCV	(fl)	87.6 (84.0-91.2)	87.9 (80.5- 90.4)	87.7 (83.9-91.0)	0.334
RDW	(fl)	13.9 (13.2-15.4)	17.1 (14.6-19.1)	13.9 (13.2-15.5)	0.002
Platelet	(10^3µ/L)	260.0 (218.0- 312.0)	237.0 (213.5- 342.5)	259.0 (218.0-313.0)	0.646
MPV	(fl)	9.3 (8.5-10.3)	9.2 (7.3-9.7)	9.3 (8.4-10.3)	0.502
ALT	(IU/L)	25.0 (16.0-79.0)	21.5 (12.2- 42.0)	25.0 (16.0- 72.0)	0.425
Albumine	(g/dL)	41.0 (36.0-44.0)	34.5 (26.8- 38.5)	41.0 (36.0- 44.0)	0.024
AST	(IU/L)	28.0 (19.0- 63.5)	47.0 (22.0-66.8)	29.0 (19.0-64.0)	0.667
CRP	(mg/L)	51.1 (9.5-153.8)	148.8 (108.0-168.5)	59.0 (11.1-161.0)	0.042
Creatinine	(mg/dL)	0.8 (0.7-1.0)	1.0 (1.0-1.8)	0.8 (0.7-1.0)	0.026
CAR		1.3 (0.2-4.3)	4.2 (2.6-6.6)	1.4 (0.3-4.4)	0.012
GPS	(Mean±SD)	0.9 ± 0.6	1.5 ± 0.5	1.0 ± 0.6	0.006
	(Range)	0.0-2.0	1.0-2.0	0.0-2.0	
mGPS	(Mean±SD)	0.9 ± 0.6	1.5 ± 0.5	0.9 ± 0.6	0.006
	(Range)	0.0-2.0	1.0-2.0	0.0-2.0	

WBC, white blood cell; MCV, mean corpuscular volume; RDW, red cell distribution width; MPV, mean platelet volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; CAR, CRP/albumin ratio; GPS, Glasgow prognostic score; mGPS, Modified Glasgow prognostic score.

The abilities of CAR, GPS, and mGPS to predict mortality were found to be statistically significant. Their AUC values were 0.73 (0.09–0.98) for CAR with a cut-off value of 3.9 (p = 0.003), 0.72 (0.10–0.97) for GPS with a cut-off value of 2 (p = 0.006), and 0.73 (0.10–0.97) for mGPS with a cut-off value of 2 (p = 0.006; Table.3).

Table 3. ROC analysis for CAR, GPS, and MODFGPS for 30-day mortality

	Cutpoint	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC	p value
CAR	3.9	70%	73.75%	9.33%	98%	0.73	0.003
GPS	2	50%	83.01%	10.20%	97.73%	0.72	0.006
mGPS	2	50%	83.01%	10.20%	97.73%	0.73	0.006

CAR, CRP/albumin ratio; GPS, Glasgow prognostic score; mGPS, Modified Glasgow prognostic score.

In the binominal logistic regression analysis with age, lymphocyte, hemoglobin, and RDW and indices; Regression analysis with CAR was named model 1, regression analysis with GPS as model 2, and regression analysis with mGPS as model 3. (Table.4)

Table 4. Binominal Logistic regression analysis

	Model 1(p value)	Model 2(p value)	Model 3
Yaş	0.021	0.034	0.035
Lymphocyte	0.669	0.686	0.685
Hemoglobin	0.204	0.192	0.193
RDW	0.828	0.930	0.928
CAR	0.301		
GPS		0.334	
mGPS			0.332

RDW, red cell distribution width; CAR, CRP/albumin ratio; GPS, Glasgow prognostic score; mGPS, Modified Glasgow prognostic score

Accordingly, age, lymphocyte, hemoglobin, RDW, CAR, GPS and mGPS in our model, which was created with these parameters to predict mortality together, had an AUC value of 0.90, sensitivity was 99%, specificity was 11%, and accuracy was 97%. (The jamovi Project 2021. Jamovi version 2.2)

4. Discussion

This study found that CAR, GPS, and mGPS could predict mortality at a good-to-moderate level in patients with acute cholecystitis. This finding shows that combined CRP and albumin indices can be used as prognostic indicators in patients with acute cholecystitis. In addition, we found that these three indices performed similarly. As expected, high neutrophil and low lymphocyte, hemoglobin, and hematocrit levels also significantly affected mortality. We observed significant independent relationships between mortality, low albumin, and high CRP levels. However, in the multivariate analysis performed with age, lymphocyte, hemoglobin, and RDW, we found that CAR, GPS and mGPS together could predict mortality well. Using CAR as an inflammation marker has previously been assessed in patients with malignancies [5]. In addition, studies have reported that CAR may be a poor prognostic marker in Crohn's disease [6] and sepsis [7]. A retrospective study examining 958 pneumonia patients found that CAR significantly predicted mortality and hospitalization [8]. However, another study found that CAR was not predictive of poor prognosis in COVID-19 patients or superior to CRP [9]. These studies [5-8] generally performed on inflammatory diseases showed that CAR is associated with mortality, while albumin and CRP also have significant independent relationships with mortality, consistent with this study.

Like CAR, GPS and mGPS have been assessed as inflammation markers, especially in patients with malignancies [10-12]. Terazawa et al. studied head and neck cancer patients and found a significant relationship between survival, low albumin, and high CRP. However, mGPS failed to predict poor prognosis in this patient group [10]. Siyu et al. reported that GPS and mGPS could act as poor prognostic indicators in patients with ovarian cancer [11]. Similarly, a meta-analysis by Nie et al. indicated that GPS and mGPS could act as poor prognostic markers in gynecological cancers [12]. In this study, GPS and mGPS were able to predict mortality, and as in many malignancies, the hospital stay was significantly longer in patients with mortality. There was also a significant relationship between age and mortality.

While acute cholecystitis is an inflammatory disease that leads to CAR, GPS, and mGPS examinations, there have been limited studies on it [13-15]. This study determined prognosis according to 30-day mortality, and CAR, GPS, and mGPS were evaluated and compared. Therefore, we believed it would contribute to the body of evidence on this topic. Karakaş et al. found no significant difference in CRP, albumin, WBC, monocytes, neutrophils, and lymphocytes in patients with complicated compared to uncomplicated acute cholecystitis. However, GPS was significantly higher in patients with

complicated cholecystitis (p = 0.020) [13]. Another study found that WBC, neutrophil, and CRP levels were significantly higher in acute cholecystitis patients with poor prognoses, while albumin was significantly lower. The same study reported that GPS could predict poor patient prognosis [14]. A retrospective study on 260 patients with acute cholecystitis found that WBC, high neutrophils, low lymphocytes, CAR, GPS, and mGPS were significant determinants of poor patient prognosis [15].

5. Conclusions

Inflammatory markers, including CRP and albumin, can predict the prognosis of patients with acute cholecystitis, as in many other diseases. Meta-analyses must confirm our results on CAR, GPS, and mGPS in patients with acute cholecystitis to minimize their mortality and improve their treatment.

Limitations

This study examined the 30-day mortality of patients. Therefore, whether a new attack developed after 30 days remains unknown. Our patient's postoperative data were not collected. Initial examinations were taken in the Emergency Department. The number of patients was limited to access the data fully.

Source of funding

There was no funding for this study.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Ethical statement

This study was approved by the Ethics Committee of the University of Health Sciences and Ümraniye Education and Research Hospital (Date: 29/09/2022, Decision No: B.l0.1.TKH.4.34.H.GP.0.01/302).

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' Contributions: Concept – H.Ş.A., H.A.; Design- H.Ş.A., E.G.; Supervision- H.Ş.A., H.A.; Resource-M.T.A.; Materials- H.Ş.A., E.G; Data Collection and/or Processing– E.G., M.T.A., H.A.; Analysis and/or Interpretation- H.Ş.A., M.T.A.; Literature Search– H.A., M.T.A.;Writing– H.Ş.A., H.A.; Critical Reviews– E.G., M.T.A., H.A.; Other- H.Ş.A., E.G.

References

[1] Yokoe, M., Hata, J., Takada, T., et al. "Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos) ", *J Hepatobiliary Pancreat Sci*, 25(1), 41-54, 2018. https://doi.org/10.1002/jhbp.515.

[2] Yeşiltaş, M., Karakaş, D.Ö., Arıbal, S., et al. "Percutaneous cholecystostomy results of 136 acute cholecystitis patients: A retrospective cohort study", *J Surg Med*, 5(9), 894-9, 2021. https://doi.org/10.28982/josam.980122.

[3] Rajab, I.M., Majerczyk, D., Olson, M.E., et al. "C-reactive protein in gallbladder diseases: diagnostic and therapeutic insights", *Biophys Rep*, 6(2-3), 49-67, 2020. https://doi.org/10.1007/s41048-020-00108-9.

[4] Wang, Y., Hu, X., Huang, Y., et al. "Prognostic value of the C-reactive protein to albumin ratio in esophageal cancer: a systematic review and meta-analysis", *Kaohsiung J Med Sci*, 36(1), 54-61, 2020. https://doi.org/ 10.1002/kjm2.12129.

[5] Kinoshita, A., Onoda, H., Imai, N., et al. "The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma", *Ann Surg Oncol*, 22, 803-10, 2015. https://doi.org/10.1245/s10434-014-4048-0.

[6] Qin, G., Tu, J., Liu, L., et al. "Serum albumin and C-reactive protein/albumin ratio are useful biomarkers of Crohn's disease activity", *Med Sci Monit*, 22, 4393-400, 2016. https://doi.org/10.12659/msm.897460.

[7] Kim, M.H., Ahn, J.Y., Song, J.E., et al. "The C-reactive protein/albumin ratio as an independent predictor of mortality in patients with severe sepsis or septic shock treated with early goal-directed therapy", *PLoS One*, 10(7), e0132109, 2015. https://doi.org/10.1371/journal.pone.0132109.

[8] Özdemir, S., Akça, H.Ş., Algın, A., Eroğlu, S.E., "Can C-reactive protein-to-albumin ratio be a predictor of short-term mortality in community-acquired pneumonia? ", *Ann Clin Anal Med*, 12(9), 1043-8, 2021. https://doi.org/10.4328/ACAM.20576.

[9] Özdemir, S., Algin, A., "Evaluation of the ability of the C-reactive protein-to-albumin ratio to predict short-term mortality in patients with COVID-19 ", *J CLIN MED KAZ*, 18(6), 35-9, 2021. https://doi.org/10.23950/jcmk/11324.

[10] Terazawa, K., Ohashi, T., Shibata, H., Ishihara, T., Ogawa, T., "Immune-modified Glasgow prognostic score: A new prognostic marker for head and neck cancer", *Head & Neck*, 1-9, 2022. https://doi.org/10.1002/hed.27170.

[11] Xu, S., Song, L., Liu, X., "Prognostic Value of Pretreatment Glasgow Prognostic Score/Modified Glasgow Prognostic Score in Ovarian Cancer: A Systematic Review and Meta-Analysis", *Nutrition and Cancer*, 74, 6, 1968-75, 2022. https://doi.org/10.1080/01635581.2021.1980591.

[12] Nie, D., Zhang, L., Wang, C., Guo, Q., Mao, X., "A high Glasgow prognostic score (GPS) or modified Glasgow Nutrition and Cancer prognostic score (mGPS) predicts poor prognosis in gynecologic cancers: a systematic review and meta-analysis", *Arch Gynecol Obstet*, 301(6), 1543–51, 2020. https://doi.org/10.1007/s00404-020-05581-8.

[13] Karakaş, D.O., Yeşiltaş, M., "Validity of the Glasgow prognostic score and modified systemic inflammation score in predicting complicated cholecystitis", *Hippokratia*, 24(1), 15-20, 2020.

[14] Cakcak, İ.E., Kula, O., "Predictive evaluation of SIRI, SII, PNI, and GPS in cholecystostomy application in patients with acute cholecystitis", *Turkish Journal of trauma and emergency surgery*, 28, 940-6, 2022. https://doi.org/10.14744/tjtes.2022.90249.

[15] Sato, N., Kinoshita, A., Imai, N., et al. "Inflammation-based prognostic scores predict disease severity in patients with acute cholecystitis", *Eur J Gastroenterol Hepatol*, 30(4), 484-9, 2018. https://doi.org/10.1097/MEG.0000000000001063.

[16] Kishiki, T., Masaki, T., Matsuoka, H., et al. "Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer", Am J Surg, 206(2):234-40, 2013. https://doi.org/ 10.1016/j.amjsurg.2012.07.051.

[17] Nozoe, T., Matono, R., Ijichi, H., Ohga, T., Ezaki, T. "Glasgow Prognostic Score (GPS) Can Be a Useful Indicator to Determine Prognosis of Patients With Colorectal Carcinoma" , International Surgery, 99(5), 512-7, 2014. https://doi.org/10.9738/INTSURG-D-13-00118.