RESEARCH ARTICLE

Validity of the Glasgow prognostic score and modified systemic inflammation score in predicting complicated cholecystitis

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Abstract

Background: Complicated cholecystitis (CC) is the severe form of acute cholecystitis (AC). Clinical, radiological, inflammatory, or biochemical parameters are used to predict presence of CC. We aimed to evaluate the Glasgow prognostic (GPS) and modified systemic inflammation scores (mSIS) that are used to predict presence of CC.

Methods: We retrospectively analyzed data from patients who underwent AC surgery from January 2014 to August 2019. Collected information included age, gender, length of stay (LOS), pathology [as CC or uncomplicated (UCC)], albumin, C-reactive protein (CRP), white blood cells (WBC), and neutrophils (NEU) results. The lymphocyte-to-monocyte ratio (LMR) was calculated. The GPS was calculated using CRP and albumin levels, and mSIS was calculated using LMR and albumin levels, and it was scored from 0 to 2.

Results: Among the 593 hospitalized patients, 217 patients underwent AC surgery and were included in the study. Among them, 40.1 % of the patients had CC, 53.4 % were male, and the mean age was 51.76 ± 13.8 years. LOS was significantly longer for CC compared to UCC (p =0.018). Four patients died from CC (1.8 %). The mean CRP, WBC, and NEU levels were not different CC compared to UCC (p =0.821, p =0.84, and p =0.196, respectively). The cut-off values for CC were 103.54 mg/L, 15.18 $\times 10^6$/μL, and 11.79 $\times 10^3$/μL, respectively. GPS and mSIS were significantly higher in CC compared to UCC (p =0.008, p =0.022, respectively).

Conclusion: CRP, WBC, and NEU could be used to predict presence of CC. The combination of CRP or LMR with albumin could be a positive but weak predictor of CC, and it is quick, easy to use, and reliable. HIPPOKRATIA 2020, 24(1): 15-20.

Keywords: Acute cholecystitis, severity, complicated cholecystitis, Glasgow prognostic score, modified systemic inflammation score

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Introduction

The prevalence of gallstone complaints was reported to be as high as 15-20 % at the general population; of these patients 2 % are admitted to hospital annually, and 20 % of them have acute cholecystitis (AC)[1]. Complicated cholecystitis (CC) (including necrotizing, gangrenous, emphysematous, or perforated cholecystitis) is the severe form of AC. CC accounts for 2-30 % of the AC, and the mortality rate varies from 0.9 to 17.8 %[2-4]. Early detection and treatment is important with CC to prevent morbidity and mortality.

Treatment for AC is considered and selected according to severity. Uncomplicated AC can be suitable for medical treatment, while complicated AC requires surgical or radiologic intervention. The Tokyo Guidelines (TG; TG13 and TG18 updates in years 2013 and 2018, respectively) or the American Association of the Surgery for Trauma (AAST) scales are the most frequently used methods to evaluate AC severity[5,6]. However, TG shows the clinical severity of AC, but not the surgical severity, and AAST scales can be used after surgery. Additionally, C-reactive protein (CRP), white blood cells (WBC), neutrophil percentage (NEU%), liver function tests, hemoglobin (Hb), platelet (PLT), and procalcitonin (PCT) are used to predict the severity of AC, but different sensitivities and specificities have been reported[7-11]. Predicting CC severity can be challenging due to laboratory or imaging results in these patients. Furthermore, some of the most frequently used inflammatory biomarkers are not adequate to predict and classify CC severity.

A low albumin level is an indicator of poor nutrition, immunity, and prognosis. The combination of albumin and inflammatory markers is a good predictor of disease severity, prognosis, or survival in CC. Hypoalbuminemia and high CRP [Glasgow prognostic score (GPS)] and hypoalbuminemia with a lower lymphocyte-to-monocyte ratio (LMR) [systemic inflammation score (SIS)] were used to predict the prognosis and survival of some cancer patients. GPS and SIS can be used to predict the severity of an inflammatory disease such as AC[12-16]. The aim of this study was to evaluate GPS and modified systemic inflammation scores (mSIS) for predicting presence of CC.

Materials and Methods

After receiving institutional approval from the Ethics Committee at Health Science University, Okmeydanı Training and Research Hospital Ethics Committee (decision No 1209, date: 02/04/2019), were retrospectively evaluated the records of all patients who underwent surgery for AC from January 2015 to August 2019. Patients treated conservatively and those who underwent surgery for malignant/premalignant pathology were excluded from the study. Patient age, gender, length of hospital stay (LOS), surgery type, comorbidities, survival, pathology [uncomplicated cholecystitis (UCC) or CC], liver function tests, albumin (g/dL), CRP (mg/L), and hemogram results were retrospectively evaluated. Type of surgery was evaluated as laparoscopic, open, or conversion to open from laparoscopic.

Alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), alkaline phosphatase (ALP) (U/L), gamma glutamyl transferase (GGT) (U/L), lactic dehydrogenase (LDH) (U/L), and total bilirubin (TBIL) (mg/dL) were evaluated as liver function tests.

Hb (g/dL), PLT (10^3/μL), WBC (10^6/μL), lymphocyte (LYMPH) (10^3/μL), monocytes (MONO) (10^3/μL), neutrophils (NEU) (10^3/μL), and NEU% were evaluated from the hemogram tests. The lymphocyte-to-monocyte ratio (LMR) was calculated by dividing the lymphocyte count by the monocyte count.

GPS was calculated using the CRP and albumin levels. When CRP was >10 mg/L and albumin was <3.5 g/dL, the GPS score was two; when only one of them met these levels, the GPS score was one; when neither met these levels, the GPS score was zero. SIS was calculated using the LMR and albumin levels. When LMR was ≤4.4 and albumin was ≤4 g/dL, the SIS score was two; when only one of them met these levels, the SIS score was one; when neither met these levels, the SIS score was zero. The mSIS is considered more scientific, and it was calculated using the albumin levels as <3.5 g/dL or >3.5 g/dL.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Age, LOS, and laboratory results were reported as the mean ± standard deviation (SD). CRP, WBC, NEU, GPS, and mSIS were evaluated using receiver operating characteristic (ROC) analysis [area under the curve (AUC); confidence interval (CI)]. The correlation of GPS and mSIS with CC was evaluated using Pearson's correlation. The data were checked for normal distribution by Kolmogorov-Smirnov test. Nonparametric values were evaluated using the Mann-Whitney U test, and parametric values evaluated using a t-test. Additionally, a p value <0.05 was accepted as significant.

Results

Among the 593 hospitalized patients, 217 underwent surgery for AC and were included in the study. Among those included, 59.9 % (n =130) had UCC and 40.1 % (n =87) had CC. The mean overall age was 51.76 ± 18.3 years, 50.65 ± 13.8 years for UCC patients, and 53.40 ± 13.76 years for CC patients. Overall, 53.4 % of the patients were male (50.7 % of UCC and 57.4 % of CC patients). There was no difference between the groups for age and gender (p =0.824, p =0.333, respectively). The overall mean LOS was 3.39 ± 3.0 days. Mean LOS was significantly lower (p =0.018) in UCC patients (2.98 ± 1.9 days) compared with CC patients (4.0 ± 4.1 days). Additionally, 80.6 % of the patients underwent laparoscopic surgery, and 11.2 % of the patients had their laparoscopic surgery converted to open surgery. The open cholecystectomy rate was higher in CC compared to UCC patients, but the difference was not statistically significant (p =0.071). The most common comorbidities in both groups were diabetes and hypertension (26 % vs 25.2 % and 22.3 % vs 21.8 %, respectively). Heart disease and chronic renal failure were significantly higher in CC compared to UCC patients (p =0.008 and p =0.033, respectively). Only four CC patients died during their hospital stay (1.8 %) (Table 1).

The mean ALT, AST, albumin, HB, and PLT levels were higher in the UCC group compared to the CC group, but the differences were not statistically significant (p =0.409, p =0.496, p =0.161, p =0.853, and p =0.41, respectively). The mean ALP, GGT, LDH, and TBIL levels were higher in the CC group compared to the UCC group, but the differences were not statistically significant (p =0.06, p =0.299, p =0.996, p =0.208, and p =0.74, respectively) (Table 2).

The mean CRP was higher in CC compared to UCC patients (171.43 ± 131.6 mg/L vs 125.77 ± 127.3 mg/L), but the difference was not statistically significant (p =0.821). The mean WBC was higher in CC compared to UCC patients (17.73 ± 6.2×10^6/μL vs 15.28 ± 5.4×10^6/μL), but the difference was not statistically significant (p =0.84). The mean MONO and NEU levels were higher in CC compared to UCC patients, and the mean LYMPH was higher in UCC compared to CC patients, but the differences were not statistically significant (p =0.469, p =0.196, and p =0.121, respectively). The mean NEU% was significantly higher in CC compared to UCC patients (80.92 ± 7.0 % vs 77.27 ± 12.3 %; p =0.001). The mean LMR was significantly lower in CC compared with UCC patients (2.02 ± 1.6 vs 2.44 ± 2.1; p =0.047; Table 2).

The mean rank of GPS was significantly higher in CC compared to UCC patients (121.16 vs 100.86; p =0.005). The mean rank of the mSIS was also significantly higher in CC compared with UCC patients (118.26 vs 102.80; p =0.022). GPS and mSIS were weakly correlated with CC (Pearson's correlation coefficient: +0.192 and +0.158; p =0.004 and p =0.02, respectively) (Table 3).

The cut-off values for CC were as follows, CRP: 103.54 mg/L, WBC: 15.18 ×10^6/μL, and NEU: 11.79 ×10^3/μL. For CC, the AUC value for the GPS was 0.594 (95 % CIs: 0.517–0.670, p =0.02), and that of mSIS was 0.571 (95 % CIs: 0.494–0.648, p =0.075) (Figure 1). The ROC analysis results are shown in Table 4.

Table 1: The demographic characteristics of the 217 uncomplicated and complicated acute cholecystitis patients that underwent surgery and were included in the study.

Parameters	Uncomplicated (n: 130)	Complicated (n: 87)	p value
Age (year)*	50.65 ± 13.8	53.40 ± 13.76	0.824
Gender			
Male	66 (50.7)	50 (57.4)	0.333
Female	64 (49.3)	37 (42.6)	
Length of Stay (days)	2.98 ± 1.9	4.00 ± 4.1	0.018
Operation Type			
Laparoscopic	110 (84.6)	65 (74.7)	0.071
Open	7 (5.4)	14 (16.1)	
Conversion to Open	13 (10)	13 (9.2)	
Comorbidities			
Diabetes	34 (26)	22 (25.2)	0.763
Hypertension	29 (22.3)	19 (21.8)	0.34
IHD/Heart Disease	12 (9.2)	13 (14.9)	0.008
COPD/Asthma	9 (6.9)	12 (13.7)	0.094
CRF	0 (0)	3 (3.4)	0.033
CVA, Epilepsy	6 (4.6)	2 (2.3)	0.88
Thyroid Disease	8 (6.1)	4 (4.6)	0.624
Cancer History	4 (3)	3 (3.4)	0.189
Others	6 (4.6)	8 (9.2)	0.179
Survival			
Alive	130 (100)	83 (98.2)	0.151
Dead	0 (0)	4 (1.8)	

Values are reported as mean ± standard deviation or as number and percentage in brackets. n: number, IHD: ischemic heart disease, COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, CVA: cerebrovascular accident.

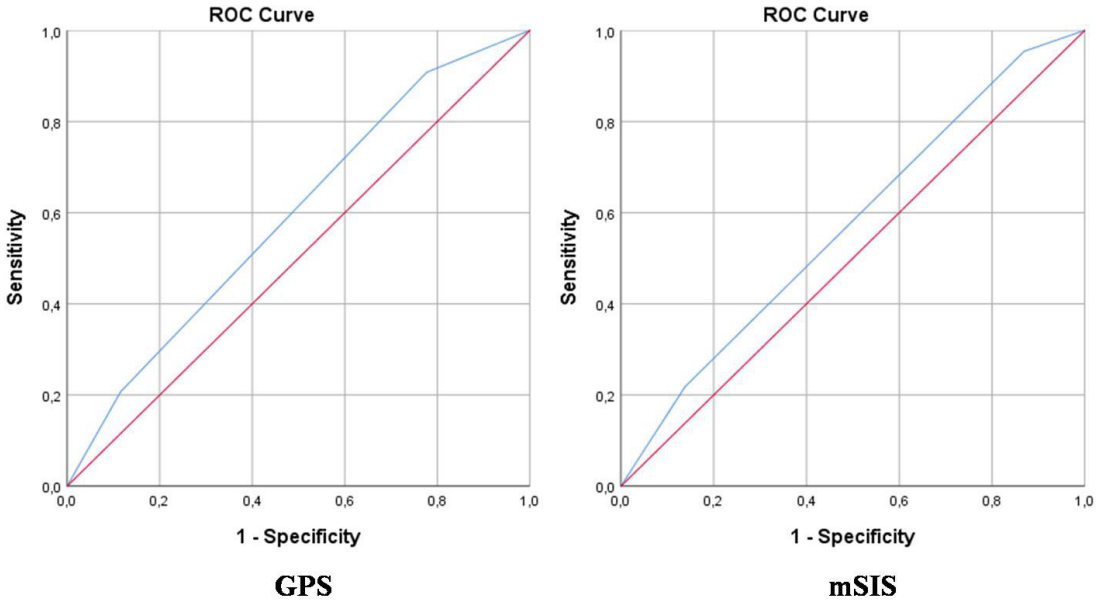

Figure 1: The using receiver operating characteristic (ROC) analysis images for Glasgow prognostic score (GPS) and modified systemic inflammation scores (mSIS) for predicting the presence of complicated cholecystitis.

Table 2: Comparison of the hematological and biochemical parameters between the 217 uncomplicated and complicated acute cholecystitis patients that underwent surgery and were included in the study.

Parameters	Uncomplicated (n: 130)	Complicated (n: 87)	p value
ALT (U/L)	36.99 ± 66.8	34.54 ± 49.5	0.409
AST (U/L)	36.05 ± 62.1	34.85 ± 49.2	0.496
ALP (U/L)	91.06 ± 54.7	100.07 ± 91.3	0.06
GGT (U/L)	55.74 ± 77.9	66.34 ± 90.8	0.299
LDH (U/L)	224.03 ± 85.4	232.16 ± 80.5	0.996
TBIL (mg/dL)	0.95 ± 0.7	1.19 ± 0.8	0.208
Hb (g/dL)	13.49 ± 1.8	13.42 ± 1.8	0.853
PLT (10^3/μL)	261.32 ± 71.3	259.25 ± 97.1	0.41
Albumin (g/dL)	4.03 ± 0.5	3.92 ± 0.6	0.161
CRP (mg/dL)	125.77 ± 127.3	171.43 ± 131.6	0.821
LYMPH (10^3/μL)	2.01 ± 1.3	1.84 ± 0.7	0.121
MONO (10^3/μL)	1.06 ± 0.6	1.19 ± 0.5	0.469
NEU (10^3/μL)	12.20 ± 5.3	14.55 ± 5.8	0.196
NEU%	77.27 ± 12.3	80.92 ± 7.0	**0.001**
WBC (10^6/μL)	15.28 ± 5.4	17.73 ± 6.2	0.84
LMR (g/dL)	2.44 ± 2.1	2.02 ± 1.6	**0.047**
GPS*	100.86 ± 13112	121.16 ± 10541	**0.005**
mSIS*	102.80 ± 13364	118.26 ± 10289	**0.022**

Values are reported as mean ± standard deviation or (*) mean rank ± sum of ranks. n: number, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP; alkaline phosphatase, GGT: gama glutamil transferase, LDH; lactat dehidrogenase, TBIL: total bilirubin, Hb: hemoglobin, PLT: platelets, WBC: white blood cells, LYMPH: lymphocytes, MONO: monocytes, NEU: neutrophils, NEU%: neutrophil percentage, LMR: lymphocyte to monocyte ratio, NLR: neutrophil to lymphocyte ratio, GPS: Glasgow prognostic score, mSIS: modified systemic inflammation score.

Table 3: Comparison of the results of the Glasgow prognostic score and modified systemic inflammation score between the groups (Pearson's correlation).

		Uncomplicated	Complicated	p value	PC	p (PC)
GPS	**0**	29	8	0.005	0.192	0.004
	1	86	61			
	2	15	18			
mSIS	**0**	17	4	0.02	0.158	0.02
	1	95	64			
	2	18	19			

GPS: Glasgow prognostic score, mSIS: modified systemic inflammation score.

Table 4: The receiver operating characteristic (ROC) analysis of the curve for C-reactive protein, white blood cells, neutrophils, Glasgow prognostic score, and modified systemic inflammation score.

	Cut Off	Sensitivity	Specificity	AUC	95 % CIs	p value
CRP (mg/L)	103.54	60.9	56.9	0.613	0.538-0.688	0.005
WBC (10^6/μL)	15.18	62.1	56.2	0.619	0.542-0.695	0.003
NEU (10^3/μL)	11.79	64.4	52.3	0.618	0.542-0.694	0.003
GPS	-	-	-	0.594	0.517-0.670	0.02
mSIS	-	-	-	0.571	0.494-0.648	0.075

CRP: C-reactive protein, WBC: white blood cells, NEU: neutrophils, GPS: Glasgow prognostic score, mSIS: modified systemic inflammation score, AUC: area under curve, CIs: confidence intervals.

Discussion

Predicting presence of CC is important to determine the patient's management strategy upon admission and decrease morbidity and mortality. Some grading systems such as TG or AAST scales were developed to predict the grade, but they did not fully show AC's surgical severity, such as development of CC. AC is an inflammatory disease of the gallbladder, and liver enzyme levels and/or inflammatory parameters are affected by inflammation. However, the increase in the severity of AC is not always correlated with variations in these parameters. WBC >18,000 μ/L indicates a moderate disease using the

TG18, but cholecystitis can be complicated even at lower WBC levels or if other inflammatory markers levels are affected. Laparoscopic cholecystectomy is generally recommended for AC, except under certain conditions. However, surgery cannot always be performed promptly due to patients' comorbidities or the adverse effect in operating schedules of weekends, holidays, or pandemics that interfere with performing in time investigative imaging studies. To predict the presence of CC, a fast, easily applicable, and reliable predictor is required.

Male gender and age >65 years are reported to be risk factors for development of CC[1,3]. A recent study showed that CC patients were most often male (57.4 %), but this difference was not statistically significant. In our study, the mean age of CC patients was 53.40 ± 13.76 years, which is younger than reported in other studies.

Conversion to open surgery has been reported to be higher for CC compared to UCC patients (14 % vs 7 %), and CC was an independent risk factor for conversion to open surgery. The LOS was significantly longer for CC compared to UCC patients based on the disease severity and open cholecystectomy[17,18]. In our study, the LOS was significantly longer for CC compared to UCC patients, but conversion to open surgery was similar between CC and UCC patients. The fact that more CC patients whose operation started with the open surgical approach could be because of the predicted CC.

WBC and CRP levels have been the most commonly used inflammatory parameters for predicting the severity of AC. Belaiv et al reported a WBC cut-off value for mild AC was 9.01 $\times 10^6/\mu L$ (68 % sensitivity, 74 % specificity) and that for moderate/severe AC was 11.05 $\times 10^6/\mu L$ (84 % sensitivity, 90 % specificity). The CRP cut-off value for mild AC was 26.5 mg/L (84 % sensitivity, 89 % specificity), and that for moderate/severe AC was 67 mg/L (96 % sensitivity, 100 % specificity). However, both parameters were not significantly different for CC patients, such as those with gangrenous and perforated cholecystitis[1]. Mok et al reported that the mean WBC and CRP levels in UCC patients were 9.1 $\times 10^6/\mu L$ and 20.6 mg/L, which were significantly higher in CC patients (14.9 $\times 10^6/\mu L$, and 331 mg/L, respectively; $p < 0.05$)[3]. Ambe et al reported significant differences for WBC and CRP levels between mild AC and moderate AC, and mild AC and severe AC, but the difference between moderate AC and severe AC was not significant[5]. In our study, the mean WBC and CRP were higher in CC compared to UCC, but the difference was not statistically significant. The WBC cut-off value was 15.18 $\times 10^6/\mu L$ (62.1 % sensitivity; 52.3 % specificity; AUC: 0.619, $p = 0.003$) for CC patients. The CRP cut-off value was 103.54 mg/L with 60.9 % sensitivity and 56.9 % specificity (AUC: 0.613, $p = 0.005$) for CC patients. Previous studies have generally included all cholecystectomy patients. Our study only included emergent cholecystectomy patients, and therefore, higher WBC or CRP levels with lower sensitivity and specificity were found for predicting CC.

CRP is a positive and albumin is negative acute-phase reactant proteins that are affected by inflammation and its severity. GPS is calculated using CRP and albumin levels. GPS predicts the prognosis in patients with lung, ovarian, colorectal, renal cancer, and hepatocellular carcinoma. CRP/albumin was reported to have a predictive effect on some inflammatory diseases such as ulcerative colitis[19,20]. Sato et al evaluated GPS and other inflammation-based markers for AC according to the TG, and suggested that they can be used as predictors for the severity of AC together with TG13[14]. However, Grade I (TG) AC pathology can be reported as 22 % necrotizing and 20 % gangrenous cholecystitis. TG13 or TG18 could predict the clinical severity, but they are inadequate for predicting AC's surgical severity[5]. In our study, the GPS score was higher for CC compared to UCC patients, and the difference was statistically significant, which was in contrast to CRP and albumin. A higher GPS could be a positive but weak predictor of CC presence.

LMR alone and SIS (LMR and albumin) were reported to be prognostic factors for survival and mortality in some cancer patients, and they were also considered as diagnostic factors for infectious diseases such as pneumonia[21-23]. In our study, the mSIS score was significantly higher, and LMR was significantly lower in CC compared to UCC patients. A higher mSIS could be a positive but weak predictor of CC presence.

The limitations of our study were its retrospective nature, derived from a single institution and for a limited period, and small sample that may explain the inability to reach statistical significance for good correlation of GPS and mSIS with CC.

In conclusion, CC is a severe form of AC, and it has a higher morbidity and mortality rate than AC. CRP >103.54 mg/L, WBC >15.18 $\times 10^6/\mu L$, and NEU >11.79 $\times 10^3/\mu L$ can be used to predict CC. The combination of CRP or LMR and albumin, which were used to calculate GPS and mSIS, are the inflammation markers. GPS and mSIS are quick, easy to use, and reliable, and they could be positive but weak predictors of CC presence.

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