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The delta neutrophil index is an early predictive marker of severe acute cholecystitis

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ABSTRACT

Background: Predicting severe acute cholecystitis (SAC) is important because the mortality rate is higher for patients with SAC than for non-SAC (NSAC) patients. We evaluated the predictive value of the delta neutrophil index (DNI), which is greater in patients with infectious and inflammatory conditions, for SAC among patients in the emergency department (ED).
Methods: This retrospective observational study included 379 consecutive adult patients with AC admitted to the ED from January 2015 to December 2016. The included patients were classified into 2 groups (NSAC and SAC) according to the Tokyo Guidelines 2018. White blood cell (WBC) count, C-reactive protein (CRP) levels, and DNI values were assessed at ED admission.
Results: The SAC group contained 28 patients (7.4%). DNI was among the early predictors of SAC and was an inflammatory marker with a significantly higher predictive value than WBC count or CRP level for detecting SAC. The predictive power of DNI was significantly higher than that of CRP when used in conjunction with WBC count, abdominal computed tomography, and clinical variables.
Conclusions: DNI measured at ED admission may serve as an early predictor of SAC.

1. Introduction

Acute cholecystitis (AC), a common complication of gallbladder stones, is one of the most common acute surgical diseases [1,2]. Although the mortality rate of AC is only around 1%, severe AC (SAC) may lead to poor prognosis [3,4]. The Tokyo Guidelines 2018 (TG18) were proposed for the risk stratification of patients with AC, with the goal of identifying indications for early cholecystectomy and useful predictors for prognosis. The TG18 classify AC into grade I (mild), II (moderate), or III (severe) [3]. Grade III (SAC) involves the presence of systemic symptoms due to organ damage and affects prognosis [3]. In a case series study of >5000 patients, the 30-day mortality for grade III patients (5.4%) was significantly higher than that for grade I (1.1%) and II (0.8%) patients [5]. SAC may require treatment in the intensive care unit (ICU) [6]. Therefore, it is important to determine disease severity early in the course of AC, as identification of patients at risk for developing SAC would facilitate administration of critical care, reducing mortality. Determination of simple, accurate, and cost-effective adjunct biomarkers for the early identification of patients who are at a high risk of developing SAC would be particularly helpful.

The delta neutrophil index (DNI) reflects the fraction of circulating immature granulocytes as the difference between leukocyte differentials measured in the cytochemical myeloperoxidase (MPO) channel and those assayed in the nuclear lobularity channel. DNI has a strong correlation with manual counts of immature granulocytes, which are elevated in patients with infectious conditions [7–9]. In sepsis, the efficacy of DNI for predicting early diagnosis, disease severity, and prognosis has been investigated [10,11]. In addition, the initial DNI value, which is used in the emergency department (ED), is useful in various gastrointestinal diseases such as acute pancreatitis, acute appendicitis, acute diverticulitis and mechanical bowel obstruction [12–16].

The DNI value is elevated up to 12 h before the onset of organ/circulatory failure in cases of severe sepsis/septic shock in medical ICUs [11]. SAC is associated with dysfunction of organs/systems. We hypothesized that DNI could predict organ dysfunction in the early phase. However, there have been no stud-

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ies on the clinical usefulness of DNI for predicting SAC using the TG18 guidelines. Therefore, we evaluated the predictive value of DNI for the presence of SAC in the ED.

2. Materials and methods

2.1. Study setting and population

This retrospective and observational study included consecutive patients aged >18 years who were diagnosed with AC in the ED of Wonju Severance Christian Hospital between January 2015 and December 2016. The ED, located in a single suburban tertiary-care hospital (Wonju, Republic of Korea), has >46,000 annual visits and board-certified emergency physicians available 24 h a day. The Institutional Review Board of Wonju Severance Christian Hospital approved this study (approval no. CR317067), and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki (1975) and its later amendments. As the study involved retrospective and observational analysis, informed consent was waived, and patient records and information were anonymized before analysis.

Computerized hospital records were reviewed, and any patients for whom 'acute cholecystitis' based on the International Classification of Diseases, 10th revision coding was used as a discharge code were initially considered for study selection. A diagnosis of AC at the ED was made when all of the following criteria were satisfied: 1) one local sign of inflammation (Murphy's sign or right upper quadrant (RUQ) tenderness/pain), 2) one systemic sign of inflammation (fever, elevated C-reactive protein (CRP) level/white blood cell (WBC) count), and 3) imaging findings characteristic of AC on abdominal computed tomography (CT) or ultrasound [3]. The diagnosis of AC was confirmed according to the pathological findings of the excised gallbladder after surgery [17].

The following patients were excluded from the study: 1) those who did not undergo any operation during admission because AC could not be confirmed on the basis of surgical and pathological findings; 2) those with hematological abnormalities or other concurrent infections (patients who received granulocyte colony-stimulating factors, glucocorticoids, or other immunosuppressants before study enrollment were also excluded because these situations can cause changes in the DNI value); 3) patients with pathological findings such as chronic cholecystitis or malignancy, or those without cholecystitis; and 4) those with insufficient data.

A total of 508 consecutive patients with AC were treated during the study period. Of these patients, 129 were excluded for the following reasons: 15 patients transferred to another hospital after conservative treatment without surgery; 25 patients had a hematological malignancy or long-term use of glucocorticoids; 62 patients had concurrent infections and inflammation, such as acute cholangitis, pancreatitis, respiratory infection, or urinary tract infection; 12 patients had a malignancy or chronic cholecystitis based on pathological findings; 9 patients needed surgical intervention but refused surgery; and 6 patients had insufficient data. Ultimately, 379 patients were included and classified into 2 groups: non-severe AC (NSAC) and SAC according to the TG18 [3].

2.2. Data collection

Data were collected through a retrospective review of patient electronic medical records performed by an emergency physician who was blinded to the study objectives and hypothesis. The evaluator was also blinded to patient group categorization and trained before data collection to reduce possible bias in the data collection process. We used specific case report forms in this study. The chart evaluator and study coordinator met periodically to resolve any disputes and review the coding rules. The study coordinator monitored the evaluator's performance.

The following data were obtained from patient medical records: age, sex, diabetes mellitus, initial vital signs (systolic blood pressure (SBP), pulse rate (PR), respiratory rate, body temperature (BT)), initial symptoms (RUQ pain or fever/chills) and symptom duration, results of abdominal physical examination (Murphy's sign or RUQ tenderness), and interpretation of complication findings, such as gangrenous or emphysematous changes, on contrast-enhanced CT scans obtained by a specialized radiologist. The presence of complications on CT scans was based on the following findings: gas in the wall or lumen, irregular wall, pericholecystic abscess, mural enhancement, pericholecystic fluid, and a considerable degree of gallbladder distension and wall thickening [18].

WBC count (ADVIA 2120i; Siemens Healthcare Diagnostics, Eschborn, Germany), CRP level (Cobas8000; Roche, Basel, Switzerland), and DNI (ADVIA 2120i, Siemens Healthcare Diagnostics) were measured during ED admission. DNI from leukocyte differentials was calculated using the following formula: DNI = (the leukocyte subfraction assayed in the MPO channel on cytochemical reaction) – (the leukocyte subfraction counted in the nuclear lobularity channel using the reflected light beam) [7]. We also investigated serum albumin and bilirubin levels (Cobas8000, Roche), which are not included in the severity grading system of TG18, but are significant factors predicting prognosis [19,20].

Abdominal CT scan, clinical variable assessment, and WBC count are routinely performed in patients with suspected AC. We further analyzed whether adding new inflammatory markers (DNI or CRP) to commonly performed elements significantly increased the ability to predict SAC. We classified models 1–3 as follows: Model 1 was a tool for predicting SAC using age, sex, SBP, PR, BT, symptom duration, fever, complications on CT, and WBC, Model 2 included all the factors in Model 1 plus DNI, and Model 3 included all the factors in Model 1 plus CRP.

2.3. Study endpoints

The primary endpoint of this study was the efficacy of DNI for predicting SAC in patients with AC admitted to the ED. The secondary endpoint was the comparative efficacy of DNI, CRP level, and WBC count in predicting SAC.

2.4. Data analysis

Normality was assessed using the Shapiro–Wilk test. Categorical variables were presented as frequencies and percentages, whereas continuous variables were presented as mean and standard deviation or as median and interquartile range. The chi-square test or Fisher's exact test was used to compare categorical variables, and the Mann–Whitney U-test was conducted to compare continuous variables. Variables with p-values of <0.05 in univariable analyses were used in the multivariable logistic regression analysis to identify early predictors of SAC. To evaluate the accuracy of predictive factors of SAC, the area under the curve (AUC) was determined using receiver operating characteristic (ROC) curves. AUC values were calculated to compare the ability of each inflammatory marker to predict SAC. The resulting statistical information was presented using forest plots. The optimal cut-off points of the factors were evaluated using ROC curves and maximum Youden index. Values of $p < 0.05$ were considered statistically significant, and analysis was performed using SPSS version 23 (IBM, Armonk, NY, USA), R version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria), and MedCalc Statistical Software version 17.5.3 (MedCalc Software, Ostend, Belgium).

Table 1
Baseline and clinical characteristics of patients with acute cholecystitis.

Variables	Total (N = 379)	NSAC (n = 351, 92.6%)	SAC (n = 28, 7.4%)	p
Age (years)	62.0 (52.0–73.0)	61.0 (51.0–72.0)	73.5 (65.3–79.3)	<0.001
Sex (male)	214 (56.5)	197 (56.1)	17 (60.7)	0.696
Diabetes mellitus	81 (21.4)	71 (20.2)	10 (35.7)	0.089
Vital signs				
SBP (mmHg)	137.0 (120.0–158.0)	140.0 (122.0–159.0)	118.5 (107.0–140.5)	<0.001
PR	83.0 (71.0–98.0)	82.0 (71.0–96.0)	101.0 (86.0–107.8)	<0.001
BT (°)	36.7 (36.4–37.2)	36.7 (36.4–37.1)	37.0 (36.5–37.7)	0.029
Symptom duration (days)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	3.0 (2.0–4.0)	0.014
Symptoms				
RUQ pain	377 (99.5)	350 (99.7)	27 (96.4)	0.142
Fever/chills	97 (25.6)	85 (24.2)	12 (42.9)	0.041
Physical examinations				
RUQ tenderness	348 (91.8)	321 (91.5)	27 (96.4)	0.716
Murphy's sign	163 (43.0)	149 (42.5)	14 (50.0)	0.437
Complication findings on CT	72 (19.0)	52 (14.8)	20 (71.4)	<0.001
Gangrenous change	72 (19.0)	52 (14.8)	20 (71.4)	<0.001
Emphysematous change	1 (0.3)	1 (0.3)	0 (0)	1.000
Pericholecystic abscess	11 (2.9)	7 (2.0)	4 (14.3)	0.006
Hepatic abscess	3 (0.8)	2 (0.6)	1 (3.6)	0.206
Biliary peritonitis	11 (2.9)	7 (2.0)	4 (14.3)	0.006
Laboratory tests				
WBC (/μL)	11.7 (8.8–15.3)	11.6 (8.8–15.0)	16.2 (10.3–20.1)	0.005
CRP (mg/dL)	5.6 (0.7–15.0)	4.1 (0.6–13.0)	18.5 (15.0–24.9)	<0.001
DNI (%)	1.0 (0.0–2.8)	0.7 (0.0–2.2)	9.1 (5.2–12.3)	<0.001
Albumin (mg/dL)	4.1 (3.7–4.4)	4.1 (3.7–4.4)	3.4 (3.0–3.9)	<0.001
Bilirubin (mg/dL)	0.9 (0.6–1.5)	0.9 (0.6–1.5)	1.8 (0.9–2.0)	0.001
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	1.4 (0.9–1.9)	<0.001
PT-INR	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.2 (1.2–1.5)	<0.001
Platelet count (/μL)	226.0 (180.0–284.0)	233.0 (185.0–288.0)	176.0 (136.8–207.5)	<0.001
Surgical methods				<0.001
Laparoscopic	293 (77.3)	285 (81.2)	8 (28.6)	
Open	86 (22.7)	66 (18.8)	20 (71.4)	
Length of hospital stay (days)	7.0 (4.0–11.0)	7.0 (4.0–10.0)	12.0 (7.3–14.8)	<0.001
ICU admission	42 (11.1)	29 (8.3)	13 (46.4)	<0.001
In-hospital mortality	5 (1.3)	2 (0.6)	3 (10.7)	0.003

Abbreviations: NSAC, non-severe acute cholecystitis; SAC, severe acute cholecystitis; SBP, systolic blood pressure; PR, pulse rate; BT, body temperature; RUQ, right upper quadrant; CT, computed tomography; WBC, white blood cells; CRP, C-reactive protein; DNI, delta neutrophil index; PT-INR, prothrombin time-international normalized ratio; ICU, intensive care unit.
Data are presented as median (interquartile range) or number (percentage).

3. Results

3.1. Characteristics of study participants

The overall median age was 62 years, and men constituted 56.5% of the study group. Approximately 21.4% of patients had diabetes mellitus. RUQ pain was the most common symptom, and RUQ tenderness was observed in 91.8% of patients. Complications of AC on CT were shown in 19% of the patients. Gangrenous change (72 patients, 19.0%) was the most common complication on CT. Laparoscopic cholecystectomy was performed in 77.3% of patients. A total of 5 patients (1.3%) died in the hospital because of pneumonia and multiple organ failure despite treatment (Table 1).

Patients were classified into the NSAC (351 patients, 92.6%) or SAC group (28 patients, 7.4%). In the SAC group, the patients were older and had longer hospital stays and higher mortality rates compared with the NSAC group. Median WBC count, CRP level, and DNI value were all significantly different between the NSAC and SAC groups (11.6/μL vs. 16.2/μL, p = 0.005; 4.1 mg/dL vs. 18.5 mg/dL, p < 0.001; 0.7% vs. 9.1%, p < 0.001, respectively) (Table 1).

3.2. Predictive value of DNI for SAC

We sought to identify early predictors for SAC. On univariable logistic regression analysis, the odds ratio (OR) of DNI to predict SAC was 2.08. Complication changes based on CT had the highest OR (OR: 14.38) among variables with p-values of <0.05 on univariable analyses. On multivariable logistic regression analysis with adjustment for age, sex, and variables with p-values of <0.05 on univariable analyses, inflammatory markers related to the development of SAC were initial DNI and serum CRP levels (OR, 1.97; 95% confidence interval (CI), 1.50–2.60, p < 0.001 and OR, 1.24; 95% CI, 1.12–1.37, p < 0.001, respectively) (Table 2). In addition, the AUC was significantly higher for initial DNI (AUC: 0.977) than for initial serum WBC count and CRP levels (AUC: 0.660 and 0.877, respectively) with respect to predicting SAC (p < 0.001 and p < 0.001, respectively) (Table 3 and Fig. 1).

Table 2
Predictors of severe acute cholecystitis on multivariable logistic regression analysis.

Variables	OR	95% CI	p
DNI	1.97	1.50–2.60	<0.001
WBC	1.07	0.99–1.16	0.092
CRP	1.24	1.12–1.37	<0.001

Variables were adjusted for age, sex, systolic blood pressure, pulse rate, body temperature, symptom duration, fever, complication findings on CT, albumin, and bilirubin.
Abbreviations: OR, odds ratio; CI, confidence interval; WBC, white blood cells; CRP, C-reactive protein; DNI, delta neutrophil index; CT, computed tomography.

3.3. Predictive model for SAC

Model 2 (Model 1 combined with DNI) was a significantly more powerful diagnostic modality than Model 1 and Model 3 (Model 1 combined with CRP). When AUCs for predicting SAC were compared, Model 2 (AUC: 0.980) had the highest diagnostic modality compared with Model 1 (AUC: 0.895) and Model 3 (AUC: 0.946)

Table 3
Diagnostic accuracy and comparison of inflammatory markers and cut-off values according to the presence of severe acute cholecystitis.

	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	p (vs. WBC)	p (vs. CRP)
WBC (/μL)	0.660 (0.610–0.707)	15.9	57.1	80.1	–	<0.001
CRP (mg/dL)	0.877 (0.839–0.908)	13.2	85.7	75.8	<0.001	–
DNI (%)	0.977 (0.956–0.990)	3.5%	100	88.0	<0.001	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; WBC, white blood cells; CRP, C-reactive protein; DNI, delta neutrophil index.

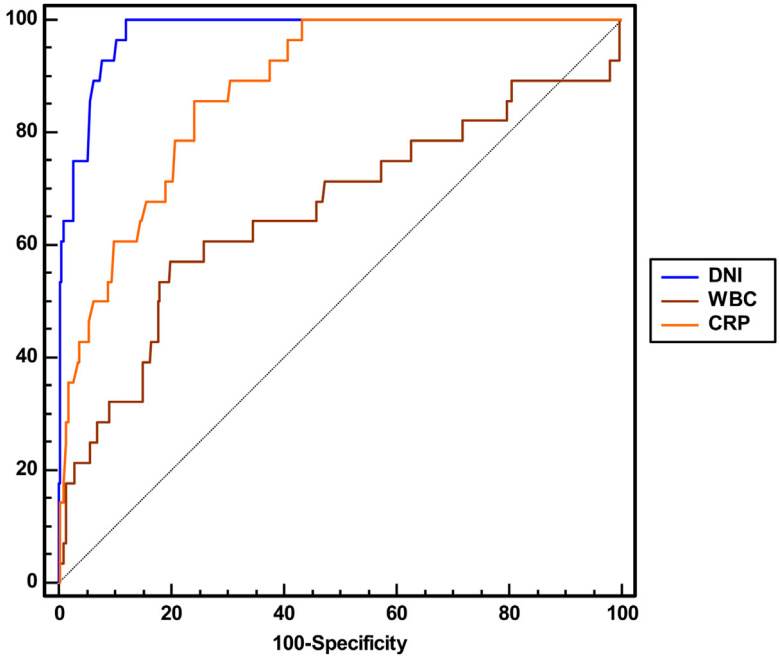

Fig. 1. Forest plot of inflammatory markers for predicting severe acute cholecystitis. The areas under the curve and 95% confidence intervals for these indicators were 0.977 (0.956–0.990) for DNI, 0.660 (0.610–0.707) for WBC count, and 0.877 (0.839–0.908) for CRP.
Abbreviations: DNI, delta neutrophil index; WBC, white blood cell; CRP, C-reactive protein.

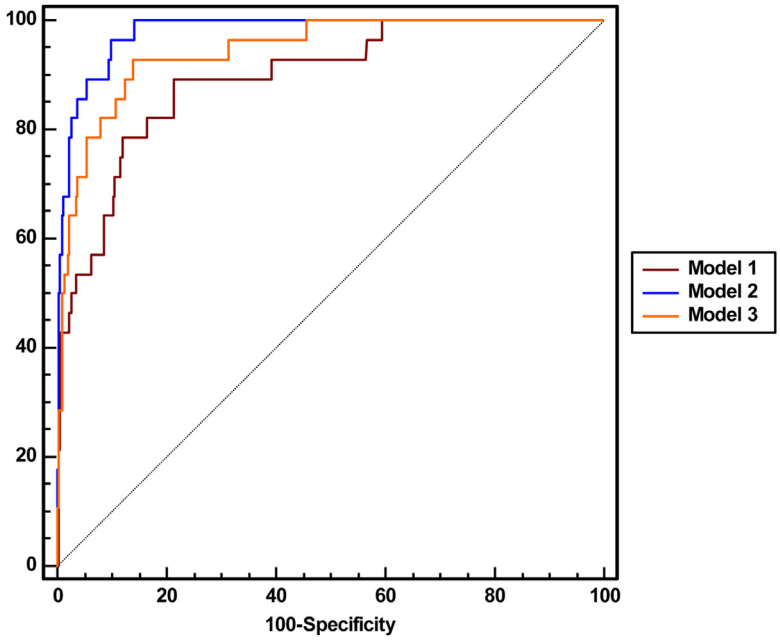

Fig. 2. Receiver operating characteristic curve of inflammatory markers combined with computed tomography findings for predicting severe acute cholecystitis.
The areas under the curve and 95% confidence intervals for the indicators were 0.980 (0.960–0.991) for DNI, 0.895 (0.860–0.924) for WBC count, and 0.946 (0.918–0.966) for CRP.
Model 1: age, sex, SBP, PR, BT, symptom duration, fever, Cx on CT, WBC.
Model 2: model 1 + DNI.
Model 3: model 1 + CRP.
Abbreviations: CT, computed tomography; DNI, delta neutrophil index; WBC, white blood cell; CRP, C-reactive protein; SBP, systolic blood pressure; PR, pulse rate; BT, body temperature; Cx, complications.

Table 4
Relationship between delta neutrophil index cut-off value and clinical parameters.

	DNI ≤ 3.5% (n = 309)	DNI > 3.5% (n = 70)	p
Severe acute cholecystitis	0 (0.0)	28 (40.0)	<0.001
Cx on CT	39 (12.6)	33 (47.1)	<0.001
Surgery methods			<0.001
Laparoscopic	257 (83.2)	36 (51.4)	
Open	52 (16.8)	34 (48.6)	
ICU admission (%)	20 (6.5)	22 (31.4)	<0.001
Total admission days	7.0 (4.0–10.0)	9.5 (6.0–13.0)	<0.001
Mortality (%)	2 (0.6)	3 (4.3)	0.046

Abbreviations: DNI, delta neutrophil index; Cx, complications; ICU, intensive care unit.
Data are presented as median (interquartile range) or number (percentage).

(Model 1 vs. Model 2, p = 0.001 and Model 2 vs. Model 3, p = 0.040) (Fig. 2).

The cut-off for DNI values was 3.5% (sensitivity, 100%; specificity, 88.0%) (Table 3). We further analyzed the relationship between DNI cut-off value and clinical variables. SAC, changes in complications based on CT scan, open surgery, ICU admission, total admission duration, ICU admission, and mortality were significantly higher in the high DNI group (DNI > 3.5%) than in the low DNI group (DNI ≤ 3.5%) (Table 4).

4. Discussion

Early prediction of SAC is important because the mortality of SAC is higher than that of NSAC [5]. In this study, DNI showed the highest predictive value compared with WBC count and CRP level for detecting the presence of SAC. The predictive power of DNI was significantly higher than that of CRP when used in conjunction with WBC count, abdominal CT scan and clinical variables. Therefore, it may be useful as an adjunct laboratory test for the early prediction of severe disease in patients with AC admitted to the ED.

The usefulness of DNI for predicting SAC may be explained as follows: 1) the number of circulating immature granulocytes will further increase when AC progresses to SAC and alterations in DNI values precede changes in the absolute number of WBCs or neutrophils because the process of granular leucocyte differentiation under infectious and inflammatory conditions starts from immature granulocyte formation [11] and 2) alterations in DNI values precede changes in CRP levels because CRP is only reliable 48 h after the onset of symptoms [21,22]. Although not investigated in this study, DNI has another advantage after admission in that it can reflect the reaction of immature granulocytes immediately after treatment, since immature granulocytes circulate for approximately 6–10 h in blood; thus, the half-life is 3–5 h. Therefore, the effects of treatment can be judged using the results of DNI from CBC measured 3 h after treatment. Furthermore, the DNI test can be performed simultaneously with routine CBC without additional time or cost, and venipuncture is performed only once.

In the TG18, a definite diagnosis of AC is made on the basis of local and systemic signs of inflammation (elevated CRP level or WBC count and fever) and imaging findings characteristic of AC, and abdominal CT scan is the recommended modality for diagnosing gangrenous and emphysematous cholecystitis [3]. In this study, the presence of complication findings on CT had the highest predictive value for SAC in univariable logistic regression. As complications including gangrenous and emphysematous changes in AC increase, the systemic inflammatory reaction progresses [23–25], after which organ dysfunction will occur. In clinical situations, CT, WBC count, and tests for additional serum inflammatory markers are commonly performed in patients with suspected AC. In this study, the combination of WBC count, interpretation of changes in complications detected on CT, clinical variables, and DNI (Model 2) was a significantly more powerful diagnostic modality than WBC count combined with CT (Model 1) and CRP levels combined with WBC count, CT, and clinical variables (Model 3) for the early prediction of SAC. This result will be useful in clinical settings.

In the TG18, WBC count is included in the differentiating criteria used for disease severity assessment [3]. In this study, although WBC count was identified as a predictive factor of SAC in patients admitted to the ED, the predictive ability of WBC count for SAC was significantly lower than that of DNI. In addition, the interpretation of WBC count may have limitations because the change from leukocytosis to leukopenia can occur as infection progresses. CRP, which is produced in hepatocytes as a response to inflammatory stimuli, is a well-known acute-phase reactant that shows increased levels in various inflammatory processes. In this study, serum CRP level differed significantly between patients with NSAC and SAC, and it was also considered an early predictive factor of SAC. Several studies have reported that CRP level is a reliable predictor of severe inflammation in AC [20,26–29]. However, an increase in CRP level may be noted after DNI increase because CRP is only reliable 48 h after the onset of symptoms [21,22]. In this study, although the SAC group had significantly longer median time from symptom onset to ED admission than the NSAC group (3.0 h vs. 2 h, p = 0.014), the predictive ability of CRP for SAC was lower than that of DNI.

SAC is more common in older patients [25], and patients with SAC were older in this study. Wang et al. [30] reported that older patients are more likely to develop SAC because they have atypical symptoms and decreased physiological defense mechanisms against gallbladder inflammation. In this study, symptom duration was significantly longer in the SAC group than in the NSAC group. It may be that because there were many elderly patients in the SAC group and they tended to show atypical symptoms, patients with SAC might have delayed their visit to the ED. Moreover, in this study, the SAC group had a significantly longer hospital stay than the NSAC group, and the ICU admission rate was significantly higher in the SAC group than in the NSAC group. Other studies have found that the length of hospital stay significantly increases for patients with a higher TG18 severity grading of AC [3,31,32]. Moreover, SAC may require treatment in the ICU [6]. Serum albumin is a significant factor predicting gangrenous cholecystitis [20] and jaundice is associated with vital prognosis in grade III cases [19]. In this study, although serum albumin and bilirubin levels were significantly different between the two groups, there were no independent predictors for early detection of SAC.

This study has several limitations. First, because of its retrospective nature, some data, such as subjective symptoms and physical examination findings, were missing or inaccurate. Second, as this study was conducted in the ED of a single hospital, the sample size was small. In addition, patient exclusion could have resulted in selection bias. Nevertheless, to reduce possible bias, we included all patients with AC admitted to the ED of this hospital during the study period. Third, we did not analyze the usefulness of DNI for evaluating treatment response by assessing changes in DNI values after definitive treatment, because serial DNI values were not determined after admission. Finally, we did not measure serum procalcitonin in all patients due to insurance problems. Despite these limitations, this study also has strengths. This is the first study to investigate the predictive value of DNI in AC. As DNI determination is fast and convenient, it can easily be performed in an ED setting. However, future prospective studies are needed to validate the results of our study.

In conclusion, DNI values measured during ED admission can be used as an early predictor of SAC. Among patients suspected of having AC with a DNI value >3.5%, intensive care and careful management should be considered during ED admission.

Conflict interest

None declared.

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