The clinical usefulness of initial serum procalcitonin as an aggravation predictor in a hepatobiliary tract infection at emergency department

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Abstract

Background and Objectives: The ability to predict future clinical deterioration early in patients who present to an emergency care center with a hepatobiliary tract infection is difficult. We studied the clinical usefulness of the initial serum levels of procalcitonin in a hepatobiliary tract infection as an indicator for predicting aggravation in the early stages.
Methods: Of the patients who presented with the clinical symptoms of a hepatobiliary tract infection, 99 were diagnosed with a hepatobiliary tract infection by imaging studies and subsequently enrolled in the study. Laboratory tests were obtained in the early stage of disease after presentation to an emergency care center. We assessed and compared the serum levels of many early inflammatory markers (white blood cell [WBC] counts, C-reactive protein and procalcitonin) between patients whose symptoms were initially stable upon arrival to an emergency care center but then deteriorated to, those whose symptoms remained consistently stable. Thus, we examined if the above serum markers are useful in predicting the possibility of future symptom aggravation.
Results: Of a total of 99 patients, 27 were assigned to the symptom aggravation group. The serum levels of WBC counts and C-reactive protein in the aggravation group were elevated. However, the median value (interquartile range) of procalcitonin was relatively increased at 2.28 (0.41–7.84 ng/ml), demonstrating a significant difference.
Conclusions: In conclusion, initial serum levels of procalcitonin might be used as an indicator for aggravation in patients with hepatobiliary tract infection at the emergency department, even though there is hemodynamic stability.

Key words: Hepatobiliary tract, infection, procalcitonin

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Introduction

The incidence of hepatobiliary tract infection is not common among the major infections in patients who visit an emergency care centers. However, hepatobiliary tract infection mortality has been reported to be relatively higher in all age groups in patients whose symptoms are aggravated following the onset of infection. In particular, the mortality rate in hepatobiliary tract infection is the second highest overall, following only urinary tract infections in elderly patients.[1] In addition, there are also some reports that the mortality rate is approximately 10–20% despite appropriate treatments in patients with bacteremia secondary to hepatobiliary tract infection.[2]

In some patients with a hepatobiliary tract infection, the symptoms were initially mild in severity upon presentation to an emergency care center; however, the symptoms

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later became suddenly aggravated. It would, therefore, be beneficial to identify indicators that predicted symptom aggravation at the earliest opportunity possible. Previous studies have considered procalcitonin, which is a known biological indicator. Procalcitonin has been previously reported to be a useful indicator for the prediction of disease severity or death in patients with pneumonia or other infectious diseases.[3] There are also some reports that serum procalcitonin levels are significantly higher in patients with sepsis or septic shock.[4-7]

However, to date, no studies have reported that procalcitonin is a useful indicator for the prediction of future symptom aggravation in the early stage when patients present to an emergency care center. Specifically, there are no reports that it is a predictor for symptom exacerbation in patients with hepatobiliary tract infections.

Given the above background, we analyzed the clinical characteristics in patients with a hepatobiliary tract infection whose symptoms were aggravated after they visited an outpatient clinic. In addition, we also examined whether baseline serum levels of procalcitonin would be useful in predicting symptom aggravation in the early stage when patients presented to an emergency care center. Furthermore, we also evaluated procalcitonin level correlation with Mortality in Emergency Department Sepsis (MEDS) and Sepsis-related Organ Failure Assessment (SOFA), both of which have previously been shown to be useful in evaluating the prognosis of patients with severe symptoms.[8-10]

Methods

Study patients and methods

The study was included 99 adult patients aged 18 years or older who visited the emergency care center of a tertiary medical center during a period ranging from May 1, 2009 to November 30, 2010 and were diagnosed with a hepatobiliary tract infection. A hepatobiliary tract infection was defined as confirmed by ultrasonography or abdominal CT scans from patients with symptoms or signs - a fever > 38°C, right upper quadrant pain, leukocytosis, hyperbilirubinemia, and increased hepatic enzymes.[11] However, we excluded patients who had a history of hepatobiliary tract surgery, those diagnosed with hepatobiliary tract cancer, those whose hepatic levels were increased due to trauma and those who had viral infections. The study was approved by the Institutional Review Board of our medical institution. The patient data were not used for other purposes besides this study. New laboratory tests were not performed during the study period. Procalcitonin testing was performed for the treatment of patients. Therefore, written informed consent was not obtained from patients in this study. After presenting to an emergency care center, a patient was classified into either the symptom aggravation group, or the stabilization group, depending on the changes in their hemodynamic status. The symptom aggravation group was composed of the patients whose systolic blood pressure remained lower than 90 mmHg for more than an hour without response to fluid therapy.[12,13] Between the two groups, we compared many known infectious markers such as white blood cell (WBC), C-reactive protein, and early serum procalcitonin.

Data collection

Through an analysis of the electronic medical records, we collected the clinical data as well as the demographic data for the current study, including age, sex, symptoms, initial vital signs, complete blood counts (CBCs) and diagnosis at hospitalization and discharge. In addition, we also evaluated many laboratory measurements such as procalcitonin, WBC and C-reactive protein that were collected immediately after the patients presented to an emergency care center. Furthermore, we also calculated the values of MEDS and SOFA based on the patient's hemodynamic profile and on the patient's CBC at the time of the outpatient visit.

Statistical analysis

Statistical analysis was performed using the SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). In comparing the mean values of the continuous variables between the two groups, we used independent sample *t*-tests if they followed a normal distribution. Otherwise, we used the Mann–Whitney U-test. All the data were expressed as the mean ± standard deviation or the median value (interquartile range [IQR]). In addition, in comparing the categorical variables, we used the Chi-square test and the Fisher's exact test. Using the receiver operating characteristic (ROC) curve and the area under the curve (AUC), we obtained the sensitivity and specificity of the markers that are used to predict the aggravation of hepatobiliary tract symptoms. A $P < 0.05$ was considered statistically significant.

Results

A total of 99 patients were divided into the stabilization group (n = 72, 72.7%) and the symptom aggravation group (n = 27, 27.3%). The mean age of all patients was 65.93 ± 14.86 years. In addition, there were 57 men (57.6%) and 42 women (42.4%). There were no significant differences in the history of disease or final diagnosis between the two groups [Table 1]. There were no significant differences in the age or sex between the two groups ($P = 0.09$, $P = 0.61$). In the early stage, when the patients presented to the emergency care center, vital signs showed that the mean systolic blood pressure was 121.32 ± 28.09 mmHg in the symptom aggravation group, which was significantly lower compared to the stabilization group ($P = 0.01$). Clinically, however, these patients did not meet diagnostic criteria for hypotension. Of all patients, 27 (27.3%) had a fever >38°C. Of these patients, 6 (19.4%) were classified into the symptom aggravation group while

21 (55.3%) were classified into the stabilization group. In addition, there were no significant differences in the mean body temperature, diastolic blood pressure, heart rate and respiratory rate between the two groups. Following hospitalization, five patients (5.0%) from the symptom aggravation group died. Upon hematologic examinations, there were no significant differences between the two groups in aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels, all of which are indicators for the functional status of the hepatobiliary tract system. However, these values were found to be significantly higher in the stabilization group. In addition, serum biochemistry analysis showed that, baseline levels of blood urine nitrogen and creatinine were 24.4 ± 21.64 and 1.50 ± 1.17, respectively, in the symptom aggravation group, and 14.55 ± 6.58 and 1.09 ± 0.71, respectively, in the stabilization group. These differences were found to be statistically significant between the two groups ($P < 0.05$) [Table 1].

Table 1: Demographic features and clinical characteristics in patient with deterioration and stable group

	Deterioration group (n=27) (%)	Stable group (n=72) (%)	P
Demographic features			
Age, mean±SD*	64.23±12.81	69.64±15.51	0.09
Sex (male/female)	17/10 (61.3%/38.7%)	40/32 (55.8%/44.1%)	0.61
Past medical history			
DM**	8 (29.6)	17 (23.6)	0.93
Hypertension	12 (44.4)	22 (30.6)	0.85
Tuberculosis	3 (11.1)	2 (2.8)	0.18
HBV# carrier (+)	1 (3.7)	4 (5.6)	1.00
Initial vital sign			
Systolic BP$	121.32±28.09	135.65±18.09	0.01
Diastolic BP	71.74±17.76	76.84±12.05	0.15
Heart rate	89.06±17.77	89.82±15.37	0.83
Respiratory rate	20.61±1.87	20.56±1.32	0.87
Body temperature	37.28±0.99	37.51±0.94	0.27
Fever (>38°C)	6 (19.4)	21 (55.3)	0.85
Blood level			
WBC§ ($10^3/\mu L$)	13.01±5.66	11.67±4.71	0.221
Hemoglobin (g/dl)	12.89±1.53	13.26±1.67	0.494
Platelet (10^9/L)	182.29±90.77	195.33±81.64	0.494
Glucose (mg/dl)	143.34±63.32	144.78±73.52	0.934
BUN§§ (mg/dl)	24.46±21.64	14.55±6.58	0.001
Creatinine (mg/dl)	1.50±1.17	1.09±0.71	0.038
AST+ (IU/L)	170.78±192.71	259.54±497.77	0.371
ALT++ (IU/L)	130.22±111.45	181.34±232.85	0.277
Tb£ (mg/dl)	2.28±1.92	2.59±2.59	0.580
Diagnosis			
Cholecystits	11 (40.7)	38 (52.8)	0.31
Cholangitis	13 (48.1)	26 (36.1)	0.22
Liver abscess	3 (9.7)	8 (11.8)	0.76

*SD=Standard deviation; **DM=Diabetes mellitus; #HBV=Hepatitis B virus; $BP=Blood pressure; §WBC=White blood cell; §§BUN=Blood urea nitrogen; +AST=Aspartate aminotransferase; ++ALT=Alanine aminotransferase; £Tb=Total bilirubin

A comparison was made between the symptom aggravation group and stabilization group of the WBC count and C-reactive protein level that were measured when the patients presented to an emergency care center. It was found that the mean WBC counts were 13.01 ± 5.66 μL in the symptom aggravation group and 11.67 ± 4.71 μL in the stabilization group. However, this difference was not statistically significant ($P > 0.05$). In addition, the median value (IQR) of the C-reactive protein levels was found to be 77.46 (14.71–161.42 mg/dl) in the symptom aggravation group, which was higher than the stabilization group. However, this difference failed to reach statistical significance ($P > 0.05$). Only the procalcitonin values showed a significant difference between the two groups; its median value (IQR) was 2.28 (0.41–7.84 ng/ml) in the symptom aggravation group ($P < 0.05$). In addition, the MEDS and SOFA results, both of which are used as indicators for the prediction of prognosis in patients with sepsis, were higher in the early stages of care in the symptom aggravation group. Moreover, the mean values of SOFA showed a significant difference between the two groups ($P < 0.05$) [Table 2].

In this study, 23 (23.2%) of all patients had positive blood cultures which yielded the following result: *Klebsiella pneumoniae*, $n = 11$ (47.8%); *Escherichia coli*, $n = 9$ (39.1%); *Streptococcus anginosus* group, $n = 1$ (4.3%); *Enterococcus faecium*, $n = 1$ (4.3%); and *Streptococcus salivarius*, $n = 1$ (4.3%). In the early stage, when the patients presented to an emergency care center, the mean levels of serum procalcitonin were significantly higher in those with positive blood cultures compared with those with negative blood cultures ($P < 0.05$) [Table 3].

Table 2: Biological findings and MEDS, SOFA score in patients with deterioration and stable group

	Deterioration group (n=27)	Stable group (n=72)	P
Procalcitonin, ng/ml (median, IQR*)	2.28 (0.41–7.84)	0.68 (0.15–2.92)	0.003
WBC, $10^3/\mu L$ (mean±SD)	13.01±5.66	11.67±4.71	0.221
CRP, mg/dl (median, IQR)	77.46 (14.71-161.42)	40.86 (6.75-117.0)	0.163
MEDS$ (mean±SD)	4.11±3.34	375±3.30	0.630
SOFA** (mean±SD)	3.44±2.53	2.25±1.88	0.012

*IQR=Interquartile range; $MEDS=Mortality in Emergency Department Sepsis; **SOFA=Sepsis-related Organ Failure Assessment; WBC=White blood cell; CRP=C-reactive protein; SD=Standard deviation

Table 3: Comparison of procalcitonin level in patients with blood culture positive or negative

	Blood culture		P
	Positive (n=26)	Negative (n=73)	
Procalcitonin (ng/ml)	2.54 (0.44-6.59)	0.67 (0.21-3.33)	0.031

Table 4: Diagnostic accuracy of procalcitonin level for indicator of deterioration patients with hepatobiliary tract infection

PCT+ level (ng/ml)	Sensitivity (%)	Specificity (%)	LR§ (+)	LR (−)	PPV* (%)	NPV** (%)
>0.2	100	28	1.38	0.00	34	100
>0.25	93	36	1.45	0.21	35	93
>0.5	70	47	1.33	0.63	33	81
>1.0	67	56	1.50	0.60	36	82
>2.0	56	68	1.74	0.65	39	80

+PCT=Procalcitonin; *PPV=Positive predictive value; **NPV=Negative predictive value; §LR=Likelihood ratio

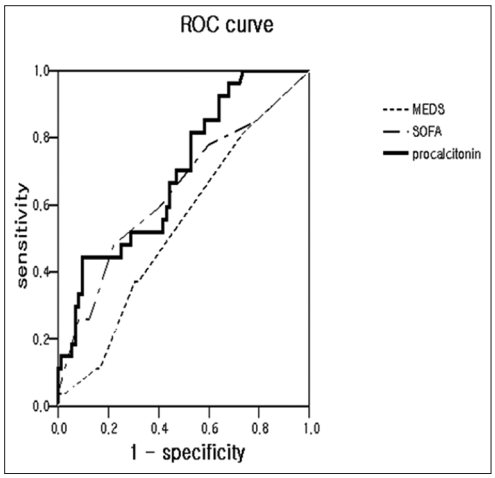

Figure 1: Receiver-operating characteristic curve for predicting between deterioration group and stable group for procalcitonin level, Mortality in Emergency Department Sepsis (MEDS) and Sepsis-related Organ Failure Assessment (SOFA) scores on initial ED visit. Area under the curve 0.694 (95% confidence interval: 0.581–0.807) for procalcitonin, 0.641 (0.513–0.769) for SOFA score, 0.537 (0.413–0.661) for MEDS score

The ROC curve analysis of the baseline procalcitonin level was performed to predict the prognosis in patients with a hepatobiliary tract infection in the symptom aggravation group that presented to an emergency care center. This analysis showed that the AUC was 0.69 (95% confidence interval: 0.59–0.78) [Figure 1]. In addition, the diagnostic accuracy based on serum levels of procalcitonin is represented in Table 4.

Discussion

In general, indicators such as MEDS, SOFA, SAPS II and APACH II are used to predict the possibility of death or the prognosis in patients with severe symptoms of an infection. These indicators have been reported to be useful for severely ill patients.[8,14-16] However, there are no reports detailing indicators that may be used to predict symptom aggravation in patients in the early stages after presentation to an emergency care center. This also applies to patients with infections whose symptoms might progress to sepsis. We therefore examined whether procalcitonin, one of the known biochemical markers for infections, would be useful as an indicator for prognosis and predicting future clinical deterioration in the early stages when patients present to an emergency care center.

Procalcitonin is a protein complex that is composed of 116 amino acids of 13-kDa in molecular weight and is a precursor hormone of calcitonin. Nijsten *et al*. reported that procalcitonin responded to bacterial or viral infections, which led to increased serum levels of procalcitonin in the early stage of infection.[17] Many studies have reported that procalcitonin is a marker for systemic infection, which can be utilized to predict the prognosis in patients with severe infection.[18,19] Park *et al*. reported that it is a useful indicator for the prediction of severe clinical deterioration and potentially death in patients with community-acquired pneumonia. In addition, Clec'h *et al*. reported that serum levels of procalcitonin were significantly higher in the intensive-care-unit (ICU) patients who were receiving medical or surgical treatments for sepsis or septic shock.[6,7] In addition, Deis *et al*. also reported that procalcitonin is a useful marker for severe bacterial infection in pediatric patients in an emergency care setting. Additionally, these authors noted that serum levels of procalcitonin were significantly increased in patients with respiratory tract infections, urinary tract infections or appendicitis.[20]

Consistent with previous reports, our results also demonstrate that serum levels of procalcitonin were relatively higher in patients with a hepatobiliary tract infection. Moreover, serum levels of procalcitonin were significantly higher in patients that were classified into the symptom aggravation group, where the clinical symptoms were initially stable but became severe following presentation to an emergency care centers, compared with the stabilization group. This indicates that the serum levels of procalcitonin would be a useful indicator for the prediction of symptom exacerbation in patients with a hepatobiliary tract infection that present to an emergency care center. By contrast, consistent with previous reports concerning infectious diseases,[5,21] WBC counts and C-reactive protein levels were also higher in patients with a hepatobiliary tract infection. However, there were no significant differences in WBC counts and C-reactive protein levels between the symptom aggravation group and the stabilization group. Clec'h *et al*. measured the serum levels of procalcitonin within a day following the diagnosis of sepsis because it is an indicator for mortality in septic patients and concluded that a cut-off value of 6 ng/ml should be used.

Moreover, other studies have also reported that the cut-off value of serum procalcitonin levels was 9.70 ng/ml and 6.00 ng/ml for the prediction of death in the survival group and the death group, respectively, following a comparison in patients with sepsis who were receiving medical and surgical treatments.[6,7] The above studies have been conducted in patients who were diagnosed with sepsis. However, no studies have examined measuring serum levels of procalcitonin to predict future symptom aggravation in the early stages of a hepatobiliary tract infection following presentation to an emergency care center. In addition, comparing MEDS and SOFA, both of which are known to be useful indicators for the prediction of death and prognosis in patients with sepsis,[8-10] with the serum levels of procalcitonin, it was found that there was no significant difference in MEDS between the symptom aggravation group and the stabilization group. It was also shown that there was a significant difference in SOFA between the two groups, but its AUC was smaller when compared to procalcitonin.

Conclusion

Initial baseline serum levels of procalcitonin might be used as an indicator for symptom aggravation in the early stages of disease onset in patients with a hepatobiliary tract infection, which differs from other markers of infection. Therefore, if the baseline serum levels of procalcitonin is elevated in a patient suspected of having a haptobiliary tract infection on presentation to an emergency care center, even if hemodynamically stable, it would be prudent to apply intensive monitoring and early treatment to prevent future symptom aggravation.

Limitations

- This study enrolled a small number of patients. It is, therefore, difficult to generalize the results of this study
- In the early stage, when the patients presented to an emergency care center, serum levels of procalcitonin were measured. However, we failed to compare the time point of the onset of symptoms and the time elapsed from the outpatient visit between the two groups. This may cause a discrepancy in the results of this study
- Therefore, further large-scale, prospective studies are warranted to further demonstrate the results of this study, which will be essential for future clinical applications.

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