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원 저

약물중독 환자에서 Neutrophil Lymphocyte Ratio의 흡인성폐렴 발생 예측인자로서의 고찰

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Neutrophil-to-lymphocyte Ratio as A Predictor of Aspiration Pneumonia in Drug Intoxication Patients

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Purpose: To evaluate the association between neutrophil-to-lymphocyte ratio (NLR) and occurrence of aspiration pneumonia in drug intoxication (DI) patients in the emergency department (ED) and to evaluate the relationship between NLR and length of hospital admission/intensive care unit (ICU) admission

Methods: A total of 466 patients diagnosed with DI in the ED from January 2016 to December 2017 were included in the analysis. The clinical and laboratory results, including NLR, were evaluated as variables. NLR was calculated as the absolute neutrophil count/absolute lymphocyte count. To evaluate the prognosis of DI, data on the development of aspiration pneumonia were obtained. Also, we evaluated the relationship between NLR and length of hospital admission and between NLR and length of ICU admission. Statistically, multivariate logistic regression analyses, receiver-operating characteristic (ROC) curve analysis, and Pearson's correlation (ρ) were performed.

Results: Among the 466 DI patients, 86 (18.5%) developed aspiration pneumonia. Multivariate logistic regression analysis revealed NLR as an independent factor in predicting aspiration pneumonia (odds ratio, 1.7; p=0.001). NLR showed excellent predictive performance for aspiration pneumonia (areas under the ROC curves, 0.815; cut-off value, 3.47; p<0.001) with a sensitivity of 86.0% and a specificity of 72.6%. No correlations between NLR and length of hospital admission (ρ=0.195) and between NLR and length of ICU admission (ρ=0.092) were observed.

Conclusion: The NLR is a simple and effective marker for predicting the occurrence of aspiration pneumonia in DI patients. Emergency physicians should be alert for aspiration pneumonia in DI patients with high NLR value (>3.47).

Key Words: Aspiration pneumonia, Neutrophil-lymphocyte ratio, Drug intoxication, Predictive factor, Emergency medicine

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INTRODUCTION

Drug intoxication (DI) is becoming an increasingly important health concern for emergency physicians. Approximately 700,000 emergency department (ED) visits are due to DI, and it has been the frequent

cause of admission to the intensive care unit (ICU) and results in significant mortality and morbidity[1-3]. Drug overdose-related death increased up to 137% between 2000 and 2014[4].

Aspiration pneumonia is a common complication of DI patients in the ED, with a reported incidence of 29%-50% in previous studies[5-7]. Aspiration pneumonia is caused by chemical injury to the lung parenchyma from the aspiration of acidic gastric contents and mainly occurs in patients with a decreased level of consciousness[8]. It can be asymptomatic or cause severe injury and result to acute respiratory distress syndrome. Although rare, aspiration pneumonia can progress to severe sepsis and death[8,9]. In the ED, the identification of patients at risk of aspiration pneumonia is essential in providing more aggressive, timely resuscitation and in planning future treatment for good prognosis.

Several risk factors have been previously reported to predict the occurrence of aspiration pneumonia such as decontamination with activated charcoal, decreased level of consciousness (LOC; low Glasgow coma scale), and opiate ingestion[10-14]. However, their applicability is limited because they need to be assessed via patient interview, which may be challenging because most DI patients are drowsy, in stupor, or present at the ED without a significant other. Particularly, it is difficult to determine the kind of medication ingested and the duration between ingestion and before medical assistance in patients with decreased LOC.

The neutrophil-to-lymphocyte ratio (NLR) has been reported as a predictive marker for various conditions such as infection, thrombotic events, and cancers[15,16]. However, to the best of our knowledge, no study has evaluated the accuracy of NLR as a predictive marker for aspiration pneumonia in DI patients in the ED. Therefore, in this study, we aimed to evaluate the association between NLR and the occurrence of aspiration pneumonia in DI patients in the ED.

METHODS

1. Study design

This study was approved by our institutional review board. This is a single-center, retrospective study based on electronic medical records (EMRs) of patients with DI in the ED. The need for informed consent was waived owing to the retrospective nature of the study.

2. Study population

Patients were recruited from January 2016 to December 2017 in a tertiary university teaching hospital that accommodates approximately 65,000 patients in the ED annually. The criteria for inclusion were as follows: 1) age 18 years or older and 2) visited the ED complaining of DI. The exclusion criteria were as follows: 1) age under 17 years, 2) incomplete EMR including lack of data on follow-up chest radiograph or chest computed tomography (CT), 3) having cancer that may influence the absolute neutrophil and absolute lymphocyte counts, including pancreatic cancer, hepatocellular cancer, or cholangiocarcinoma; and 4) having infectious conditions that might influence the NLR such as gastroenteritis, upper respiratory infection, pneumonia, or urinary tract infection.

3. Data collection and outcome measurements

One board-certified emergency physician collected data from the eligible patients' EMR, including demographics such as sex and age; past medical history such as cardiovascular, pulmonary, neurologic or psychologic disorder; clinical manifestations such as mental status, systolic and diastolic blood pressures, pulse rate, and body temperature upon ED admission; laboratory results including white blood cell (WBC) count, neutrophil count, lymphocyte count, calculated NLR, hemoglobin, platelet, albumin, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, serum glucose, serum blood-urea-nitrogen (BUN), serum creatinine, and arterial blood gas analysis; and the clinical progress of the patients including the need for gastric

lavage, activated charcoal usage, length of hospital admission in days, in-hospital mortality, and ICU admission.

Aspiration pneumonia was determined according to the chest radiograph or chest CT image obtained by a board-certified radiologist within 5 days after ED admission. If the patient was discharged after prompt treatment, the chest radiograph or chest CT findings were used on their follow-up visits. Both radiographs and CT images were interpreted by a board-certified radiologist.

NLR was calculated as the absolute neutrophil count/absolute lymphocyte count, while the duration of hospital admission was defined as the number of days from ED admission to discharge or from ED admission to patient death. In-hospital mortality referred to death while the patient was admitted. ICU admission was defined as admission to the ICU from the ED.

4. Statistical analysis

Three factors were evaluated statistically. First, multivariate logistic regression analysis was performed to determine independent factors for the development of the aspiration pneumonia in DI patients. Variables found to be statistically significant on univariate analysis were entered into the multivariate logistic regression analysis. The adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were generated from multivariate analyses. Second, a receiver operating characteristic (ROC) curve analysis (including cut-off values for optimal area under the curve (AUC), sensitivity, and specificity) was performed to identify the diagnostic performance of the independent significant variables for the prediction of aspiration pneumonia. Third, the correlation coefficient (ρ, rho) between NLR and length of hospital admission and between NLR and length of ICU admission was calculated using Pearson' s correlation. The Pearson' s correlation coefficient was interpreted as follows: ⟨0.2: none; 0.21-0.5: weak; 0.51-0.8: moderate; and ⟩0.81: strong. Meanwhile, p⟨0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline characteristics

A total of 466 DI patients were enrolled in the study. The baseline characteristics of the patients are presented in Table 1. The mean age was 51.9±19.1 years, and 33.9% of them were men. The mean length of hospital admission was 1.5±5.4 days, and the mean length of ICU admission was 0.5±2.5 days. The mean NLR was 3.2. Among the 466 patients, 86 (18.5%) developed aspiration pneumonia after admission. In terms of treatment, 176 patients (37.8%) were treated with lavage, while 200 (42.9%) were treated with activated charcoal.

2. Factors associated with the development of aspiration pneumonia

The associations between the development of aspiration pneumonia and clinical variables are shown in Table 1. In the univariate analysis, sex (p=0.002), age (p=0.005), respiration rate (p=0.034), hemoglobin (p=0.020), leukocyte (p⟨0.001), neutrophil (p⟨0.001), lymphocyte (p⟨0.001), NLR (p⟨0.001), BUN (p=0.004), and creatinine (p=0.014) were significantly different.

The independent factors for the development of aspiration pneumonia in DI patients as determined via multivariate analysis are shown in Table 2. The multivariate analysis demonstrated a significant difference in NLR (p=0.001; OR, 1.7; 95% CI, 1.4-2.0); as NLR increased, the risk of aspiration pneumonia increased 1.7-fold. Other variables were not significant.

3. Predictive performance of NLR for the development of aspiration pneumonia

The ROC curves for NLR for the prediction of aspiration pneumonia in DI patients during hospitalization are shown in Figure 1. The AUC of NLR for the prediction of survival was 0.815 (95% CI, 0.777-0.849). An NLR cut-off value of 3.47 showed a sensitivity and specificity of 86.0% (95% CI, 76.9-92.6) and 72.6% (95% CI, 67.9-77.1), respectively, for predicting the development of aspiration pneumonia.

Table 1. Patients' demographic characteristics and results of univariate analysis
Data are presented as mean±standard deviation or number of patients with proportion in parenthesis.

Characteristics	Total (n=466)	Aspiration pneumonia (n=86)	Non-aspiration pneumonia (n=380)	*p*-value
Sex (men:women)	158:308	42:44	116:264	0.002
Age	51.9±19.1	57.1±20.1	50.7±18.7	0.005
Systolic blood pressure (mmHg)	126.7±28.5	125.6±24.7	127.0±29.3	0.676
Diastolic blood pressure (mmHg)	74.3±15.9	75.6±14.7	47.0±16.1	0.410
Purse rate (/min)	88.1±20.1	88.3±21.2	88.1±19.9	0.642
Respiration rate (/min)	20.5±3.2	19.9±3.1	20.7±3.2	0.034
Body temperature (˚C)	36.4±0.7	36.4±1.2	36.4±0.5	0.603
Mental status				
Alert	249 (53.4)	41 (47.7)	208 (54.7)	0.069
Verbally responsive	127 (27.3)	21 (24.4)	106 (27.9)	0.704
Painful response	89 (19.1)	24 (27.9)	65 (17.1)	0.211
Unresponsive	1 (0.2)	0 (0)	1 (0.3)	0.070
Gastric lavage performed	176 (37.8)	28 (32.6)	148 (38.9)	0.325
Activated charcoal administration	200 (42.9)	30 (34.9)	170 (44.7)	0.060
Hemoglobin(g/dL)	13.5±1.8	13.9±1.9	13.4±1.7	0.020
Leukocyte (10^9/L)	8.4±3.7	11.2±5.5	7.8±2.9	<0.001
Lymphocyte (10^9/L)	2.4±1.3	1.5±0.8	2.6±1.3	<0.001
Neutrophil (10^9/L)	5.8±3.5	8.9±4.4	5.2±2.3	<0.001
Neutrophil-to-lymphocyte ratio	3.5±3.9	8.0±5.2	2.5±2.3	<0.001
Platelet (10^9/L)	242.8±66.8	240.1±83.9	243.4±62.3	0.677
Blood urea nitrogen (mg/dL)	14.3±8.3	17.7±12.7	13.5±6.7	0.004
Creatinine (mg/dL)	0.8±0.4	1.0±0.4	0.8±0.5	0.014
C-reactive protein (mg/dL)	0.7±2.1	1.3±3.4	0.5±1.6	0.055
Glucose (mg/dL)	150.2±45.4	156.6±44.4	145.3±46.1	0.069
Aspartate aminotransferase (IU/L)	37.0±63.7	40.0±33.4	36.3±68.8	0.633
Alanine aminotransferase (IU/L)	21.9±28.0	25.3±23.3	21.2±29.0	0.213
Arterial blood gas analysis				
pH	7.4±0.1	7.4±0.1	7.40±0.1	0.549
PO^2	87.3±24.5	83.3±23.4	88.2±24.7	0.090
PCO^2	40.2±8.5	39.8±8.1	40.3±8.6	0.627
Hospital length	1.5±5.4	4.0±7.8	1.2±4.5	<0.001
ICU* length	0.5±2.5	1.3±4.7	0.3±1.5	<0.001
Admission				
General ward	60 (12.9)	24 (28.0)	36 (9.5)	<0.001
Intensive care unit	24 (5.2)	7 (8.1)	17 (4.5)	0.27
Discharge	382 (82.0)	55 (64.0)	327 (86.1)	<0.001

p-values in boldface indicate significance ($p<0.05$). ICU*: intensive care unit

4. Relation between NLR and length of hospital admission and between NLR and length of ICU admission

No correlation between NLR and length of hospital admission (ρ=0.495) and between NLR and length of ICU admission (ρ=0.570) was observed.

DISCUSSION

In the current study, NLR showed a positive correlation with the occurrence of aspiration pneumonia in DI patients. Also, NLR was the only factor to predict the risk of aspiration pneumonia in DI patients. Several other studies predicted the severity and prognosis of aspiration pneumonia according to laboratory findings such as elevated levels of serum lactic acid, WBC count,

Table 2. Multivariate analysis for prediction of the development of aspiration pneumonia

	B*	Odds ratio (95% confidence interval)	*p*-value
Sex			0.091
Age			0.940
Respiration rate	-0.15	0.9 (0.8-1.0)	0.041
Hemoglobin			0.180
Leukocyte			0.452
Neutrophil-to-lymphocyte ratio	0.50	1.7 (1.4-2.0)	<0.001
Blood-urea-nitrogen			0.590
Creatinine			0.717
Length of hospital admission			0.495
Length of ICU⁺ admission			0.570
Admission			0.388

p-values in boldface indicate significance ($p<0.05$).
*: regression coefficient, ⁺: intensive care unit

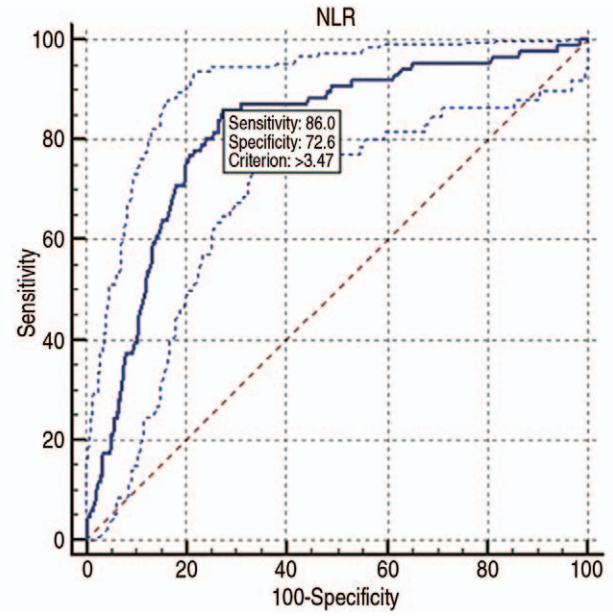

Fig. 1. Receiver-operating characteristic (ROC) curves for predicting the occurrence of aspiration pneumonia in drug intoxication patients [area under the ROC curve (solid blue line), 0.815; 95% confidence interval (dotted blue line), 0.777-0.849). Red line indicates reference line. NLR=neutrophil-to-lymphocyte ratio

and C-reactive protein[10,17,18]. In addition, gastric lavage and the administration of activated charcoal did not show significant association with aspiration pneumonia in the present study, which is consistent with the findings of previous reports[13,18]. Geoffrey et al reported that age, vomiting, and interval time from ingestion to ED arrival are correlated with the occurrence of aspiration pneumonia in DI patients[13]. We did not assess time interval in this study, while age and vomiting did not show significant correlation with aspiration pneumonia. We considered aspiration pneumonia to be the same as aspiration pneumonitis because there was no clinical difference in its occurrence in DI patients. This may have caused the difference between the findings of the current study to that of previous studies[5,8,10,13,18].

Studies that predict the occurrence of aspiration pneumonia in DI patients are limited. To the best of our knowledge, this is the first study to evaluate the predictive performance of NLR for the occurrence of aspiration pneumonia. In this present study, we demonstrated that NLR has a high predictive performance for the occurrence aspiration pneumonia in DI patients. Although, NLR did not predict patients' mortality, prolonged admission, or ICU admission, emergency physicians should be alert for aspiration pneumonia in DI patients with high NLR on the ED to provide prompt management. Moreover, emergency physicians should inform patients and their significant others about the late symptoms of aspiration pneumonia to prevent its progression.

The activation of neutrophils acts as a host defense system in inflammatory reaction such as systemic inflammatory response syndrome. Phagocytosis plays an important role by directly killing the pathogens and releasing various cytokines, granule enzymes, and reactive oxygen species. However, extremely high lev-

els of cytokines might lead to the destruction of the innate immune system, resulting in tissue damage that may lead to septic shock and organ failure. Such fatal occurrences are prevented via immunosuppression. Along with other various anti-inflammatory cytokines, lymphocytes act as immunosuppressors by inducing apoptosis. NLR is a biomarker of the balance between our immune system and immunosuppression system in patients with inflammatory reaction. Elevated NLR, which is an elevated neutrophil count and a decreased lymphocyte count, might indicate an imbalance between the immune and immunosuppression systems. An elevated NLR is a known predictor of mortality in patients with sepsis[19-22]. Furthermore, elevated NLR also reflects poor prognosis in other inflammatory conditions and thrombotic events such as myocardial infarction, meningitis, stroke, pulmonary embolism, and cancers[23-29].

Aspiration pneumonia is the result of an inflammatory reaction. In this study, a progressing activated inflammatory reaction can cause an elevated NLR. Although NLR was not associated with patients' prognosis in the current study, it was a predictive factor for the occurrence of aspiration pneumonia, making NLR an important biomarker because aspiration pneumonia in DI patients require prompt treatment to prevent septic shock and death.

Determining the NLR is simple and does not incur any additional costs. The NLR is readily accessible in any ED that can measure complete blood cell counts. Calculating the NLR in DI patients is essential as it can help identify those at high risk of aspiration pneumonia.

There are several limitations in this study including its retrospective, single-center design. Furthermore, this study was conducted based on EMR and differences in patient management such as the use of gastric lavage and activated charcoal, which may influence outcomes, was not considered. In addition, there are difference between physicians' experience (attendings, residents, interns) and way of documentation, there are inconsistent and lack of reliabilities with variables such as initial mental status, time to ED arrival time from ingestion, pH of vomitus. Therefore, we included objective valuables including laboratory findings, order of activated charcoal or gastric lavage, whether admission or not. This might have influenced our results and thus they should be interpreted with caution. In addition, only select patients who were admitted to ED for DI were included in the analysis. Therefore, some important data may have been missed. Third, the kind and amount of drugs ingested may have varied between patients, but this was not considered in the analysis. As such, our results should be validated in prospective, multi-center studies with adequate follow-up periods.

CONCLUSION

NLR showed a positive correlation with the occurrence of aspiration pneumonia in DI patients and also demonstrated predictive risk factor of aspiration pneumonia in DI patients. Therefore we recommend calculating NLR in DI patients in ED and maintain high alert to higher NLR patients occurring aspiration pneumonia.

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