DOI: 10.4149/BLL_2021_069

Bratisl Med J 2021; 122 (6)
418 – 423

CLINICAL STUDY

Comparison of inflammation markers with prediction scores in patients with community-acquired pneumonia

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ABSTRACT

OBJECTIVE: The lymphocyte-to-C-reactive protein ratio (LCRP) and Systemic Immune-Inflammation Index (SII) can successfully predict 28-day mortality rates with community-acquired pneumonia

METHODS: This prospective study was conducted in 2018. Hospitalized patients underwent follow-up evaluations 28 days after admission.

RESULTS: A total of 345 patients with CAP were enrolled in this study. All-cause mortality at the 28th day of follow-up was 13.6 %. There were statistically significant results between the 2 groups (survivors and non-survivors), in terms of the LCRP, SII, PSI, and CURB-65 values. Moreover, the optimal LCRP cutoff for predicting 28-day mortality was determined to be 4, with 89 % sensitivity, 73 % specificity. Based on the average SII>3551for predicting 28-day mortality, the sensitivity, specificity was 63.8 %, 68.1 % respectively. When the value of the cutoff PSI was ≥130 points, the sensitivity, specificity was 68 %, 65 %, respectively. Based on 3 points and above as the cutoff value of the CURB-65 score, the sensitivity, specificity was 80 %, 68 %, respectively.

ROC curve analysis revealed that the areas of LCRP, SII, PSI, and CURB-65 under the AUC in terms of 28-day mortality were 0,820,0,737,681, and 0,773, respectively,

CONCLUSIONS: LCRP and SII level are valuable for predicting the mortality rate among patients with CAP at ED admission *(Tab. 3, Fig. 3, Ref. 27)*. Text in PDF *www.elis.sk*

KEY WORDS: community-acquired pneumonia, respiratory tract infection, prediction scores, lymphocyte to CRP ratio, systemic immune-inflammation index, mortality.

Introduction

Community-acquired pneumonia (CAP) causes a significant portion of treatment expenses, work-training day losses, and deaths recorded in the daily lives of residents in a community (1). It is a fatal, infectious disease with high treatment costs despite effective therapies. Moreover, CAP remains common in developed countries and continues to be a serious health problem due to the associated morbidity and mortality. According to the US data, >4 million new CAP cases are detected annually and 15 % of these require hospitalization (2–4). In Turkey, the lower respiratory tract infections rank 5th among the leading causes of death (4.2 %) (5). Thus, CAP remains to be an important problem in everyday medical practice all over the world.

Many prediction scores have been developed for classifying CAP and determining the indications for hospitalization and intensive care need. Of these, the most widely used prediction scores in many hospitals are confusion, urea, respiratory rate, blood pressure, age >65 years (CURB-65) and pneumonia severity index (PSI). In addition to these prediction scores, developing a scoring system that determines the severity, morbidity, and mortality of the disease using laboratory parameters can assist clinicians. Neutrophils, neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and C-reactive protein (CRP) values, and their relationships with mortality have been studied (6–8). There are also markers of infection that have not been investigated. For example, systemic immune inflammation index (SII), which is an inflammation-related index, is a comprehensive combination based on the counting's of peripheral lymphocytes, neutrophils, and platelets. The formula of SII index is as follows: SII=platelet count×neutrophil/lymphocyte count and the lymphocyte-to-C-reactive protein ratio (LCRP) (calculated by dividing the lymphocyte value by the CRP value) (9).

This study aims to determine the inflammation markers in surviving and non-surviving patients with CAP and investigate whether these markers correlate with CAP prediction scores and can successfully predict 28-day mortality rates.

Material and method

Study design and setting

This single-center, cohort study was conducted at Mugla Sitki Kocman University Training and Research Hospital with 570 beds.

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A daily average of 500–650 patients are admitted via ambulance or outpatient treatment to our emergency department (ED). Before conducting the study, approval was obtained from the University Human Research Ethics Committee (No: 190147). We retrospectively investigated the clinical and laboratory findings of patients admitted to our hospital ED between January 1 and December 31, 2018.

Definitions and clinical scoring tools

CAP was defined as the presence of new pulmonary infiltrates on chest imaging and with symptoms consistent with those of pneumonia, including cough with or without sputum production, dyspnea, and fever and/or pleuritic chest pain, none of which were acquired in a hospital. Hospital-acquired pneumonia (HAP) was defined as pneumonia that occurs at ≥ 48 hours after admission and was absent during admission. Healthcare-associated pneumonia (HCAP) was defined for patients who (1) had undergone hospitalization (≥ 2 days), home infusion therapy (including antibiotics), and/or home wound care in the preceding 90 days; (2) had undergone chronic dialysis within the last 30 days; (3) were residents of nursing homes or extended care facilities; and/or (4) had family members with multidrug-resistant pathogens (10).

The severity of CAP was evaluated using the following parameters: confusion, urea (≥7 mmol/L (19 mg/dL)), respiratory rate (≥30 breaths/min), blood pressure (systolic blood pressure ≤90 mm Hg and/or diastolic blood pressure ≤60 mm Hg), age >65 years (CURB-65) (years), and PSI scores (11).

Selection of participants

We also examined the data of those who were hospitalized in the chest diseases ward or the intensive care unit (ICU) with the diagnosis of CAP between January 1 and December 31, 2018. A list of the patients diagnosed and examined with the pneumonia codes J10, J12, J15, J17, and J18 from the hospital's Department of Information Technologies was obtained and both their files and imaging data were retrospectively examined.

The inclusion criteria were as follows: aged >18 years, diagnosed with CAP, and hospitalized. The exclusion criteria included those aged < 18 years; pregnant; diagnosed with HAP, HCAP, or aspiration pneumonia; with known HIV positivity; with a history of hematological disorders or immunosuppression (usage of immunosuppressive drugs within 90 days, solid organ transplantation and and receiving ≥ 10 mg/d prednisolone or equivalent for <14 days); diagnosed with active pulmonary tuberculosis; with rheumatic disease; and those who underwent a recent blood transfusion.

Study protocol and follow-up evaluation

In our hospital, as a general practice, these patients are evaluated by an emergency medicine specialist after being ED admission. Complete blood count; glucose, kidney, and liver function tests; and electrolytes and CRP examinations are requested, a chest radiograph is captured, CURB-65 and PSI are calculated.

The patients evaluated by a pulmonologist are hospitalized based on laboratory tests, in addition to prediction scores and social indications (living alone, patients with care problems, or patients with comorbidity). Hospitalizations are planned as ward or ICU by the pulmonologist who evaluated the patient; furthermore, the parameters used for hospitalization were used for ward or ICU hospitalization indication.

These data were saved in the patients' files and on the hospital automation system. Thus, the data of the patients were accessed from the automation hospital system and individual patient files.

Data collection

For each patient, one senior emergency medicine resident who was blinded to the study objectives and hypothesis manually abstracted all data (demographics, clinical characteristics, hemodynamic parameters, laboratory test results, treatment methods, and outcomes) from the clinician notes or medical history sections within the electronic health record, entered them into a standardized chart abstraction tool, and imported the data into SPSS 22.0 (SPSS, Inc, Chicago, IL) for statistical analyses. Because the laboratory markers and severity scores were studied routinely in the daily practice of our hospital for hospitalized patients, no missing data was found. Data were retrospectively collected from medical records and reviewed. A form was created to be filled for each patient individually. The form included the following parameters: patient's age, gender, laboratory values of the blood samples obtained in the ED (neutrophil value, lymphocyte value, platelet value, and CRP value), CURB-65 and PSI scores calculated in the ED, blood taken NLR, LCRP, SII and PLR (calculated by dividing the platelet value by the lymphocyte value) are also calculated and recorded.

Patients were followed up 28 days after pneumonia diagnosis. The following details were recorded during hospitalization: where the patient was hospitalized (ICU or ward), whether intubation was performed, treatment with vasopressors, length of stay (LOS) in the hospital, intensive care hospitalization, and all-cause 28-day mortality rate.

The mortality of the patients discharged, whether there was readmission in the hospital system, and the phone number provided during the hospital registration were determined by telephone. Those who lived for 28 days were grouped as "'survivors" and those who died within 28 days were grouped as "non-survivors."

Laboratory methods

The blood test results of the patients at their first admissions to the ED of our hospital were reviewed. During the study, blood samples were drawn into tubes containing sodium citrate and analyzed under room temperature using Pentra DF Nexus, Hariba Medical device in the biochemistry laboratory. These blood samples were analyzed for the following: neutrophil count (neutrophil) (2–12 K/mL), lymphocyte count (lymphocyte) (1–4.9 K/mL), platelet (plt) (156–373 103/uL), and CRP (0-5 mg/L).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL). A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Parametric tests (Independent 0 samples t-test and post hoc Tukey test) were applied to the data of normal

Tab. 1. The statistical results of the groups according to their final status (survivors-non-survivors) 28-days later.

	Survivors n:298 (%86.4)	Non-survivors n:47 (%13.6)	Total n:345 (%100)	p
Age (years old)	69.33±14.9	72.80±10.7	69.81±14.4	≥0.05
Gender (F/M)	86/212	21/26	107/238	≤0.05
ICU stay period (day) (min-max)	1.07(0- 41)	6.10(0-22)	1.76(0-41)	≤0.05
Vasopressors need (cases)	14	24	38	≤0.05
LOS (day)	9±7	10±8	9±7	≥0.05
intubated patient (cases)	13	20	33	≤0.05
The place to stay (ICU/Ward)	22/276	37/10	59/286	≤0.05
CURB-65:(0-1 point:/2 point:/3-5 point:)	127/77/94	2/7/38	129/84/132	≤0.05
PSI:(70 point ≤:/70-130 point:/130 point≥:)	32/166/104	0/15/32	28/181/136	≤0.05
Neutrophil (K/mL)	11417±6954	14267±6440	11805 ±6947	≤0.05
Lymphocyte (K/mL)	1151±701	764±399	1099±681	≤0.05
CRP (mg/L)	171±77	303±85	189±90	≤0.05
NLR	14.7±1.5	22.2±1.2	15.7±1.5	≤0.05
PLR	0.3±0.2	0.4±0.3	0..3±0.2	≤0.05
LCRP	8.8±1.0	2.5±1.9	8.1±1.0	≤0.05
SII median(min-max)	3550(65-33036)	5761(34-25427)	3551(34-33036)	≤0.05

distribution, and non-parametric tests (Mann-Whitney U-test and Kruskal-Wallis test) were applied to the data of questionable normal distribution. Continuous data were presented as mean ± standard deviation or median (minimum-maximum), as appropriate. All differences associated with a chance probability of ≤0.05 were considered statistically significant. The area under the ROC curve was calculated to evaluate diagnostic accuracy. The cumulative survival rate was calculated using the Kaplan–Meier method, and differences in survival between the groups were compared using the Mantel–Cox log-rank test. To identify variables associated with 28-day mortality, data were initially analyzed via univariate analysis. Significant variables were subsequently used for stepwise forward logistic regression analysis. Furthermore, sensitivity and specificity were evaluated for mortality using the data.

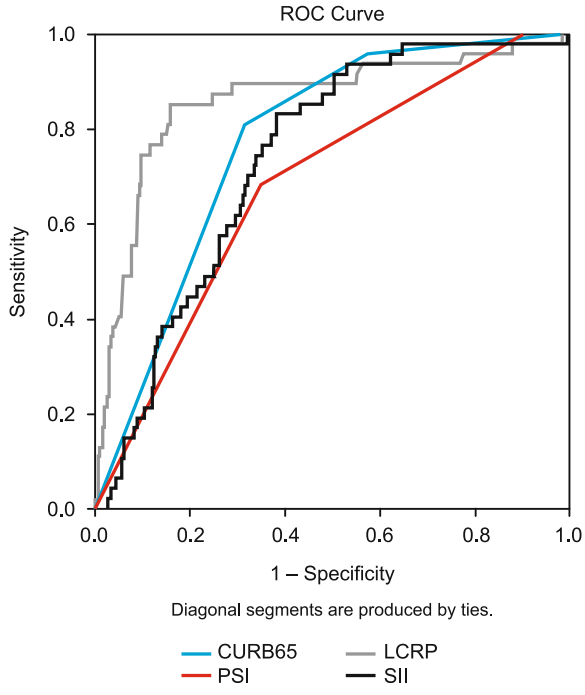

Fig. 1. Roc analysis showing the relationship of CURB-65, PSI, LCRP and SII with 28-day mortality.

Results

In our study, 382 patients presenting to the ED with a diagnosis of pneumonia were enrolled. Of these, 9 were excluded due to HCAP, 8 were excluded due to HAP, 3 were excluded because they were pregnant, 10 were excluded because they were immunocompromised, and 7 were excluded because they had rheumatic diseases. After exclusions, the complete 28-day follow-up status was available for 345 patients with a diagnosis of CAP. Among these, 107 (31 %) were women and the mean age was 69.6± 14.4 years. Moreover, 33 (9.6 %) of the patients were intubated in the emergency service, 59 (17.1 %) were hospitalized in the ICU, 38 (11 %) patients needed inotropic support as long as they stayed in the hospital, and the average LOS was 9.9± 7.6 days. In-hospital mortality was recorded for 36 (11 %) patients and 28-day mortality was recorded for 47 (13.6 %) (Tab. 1). The laboratory values of the patients are also given in Table 1.

When the patients were divided into 2 groups as “survivors” and “non-survivors” according to their condition after 28 days and then compared, significant statistical differences were observed in terms of gender, ICU stay period, needed vasopressors support, intubated in the emergency service, hospitalized in the ICU, CURB-65, PSI, neutrophil, lymphocyte, CRP, NLR, PLR, SII and LCRP ($p \leq 0.05$). However, LOS in the hospital and age did not differ significantly ($p \geq 0.05$) (Table 1). In the mean analysis to examine these statistical differences, we observed that mortality increased based on CURB-65, PSI, CRP, neutrophil, SII and prediction scores, ICU stay period, intubation in emergency, increasing vasopressors requirement, and decreasing LCRP value (Tab. 1).

With ROC curve analysis, when LCRP, SII, PSI, and CURB-65 were applied, we found that the closer the area under AUC is to 1, the more valuable the marker is. In the ROC curve analysis of the data, the areas of LCRP, SII, PSI, and CURB-65 under the

Tab. 2. Sensitivity and specificity in terms of mortality when LCRP ≤4, PSI ≥130 point, CURB 65 ≥3 point, SII>3551 are taken.

LCRP≤4	Mortality Yes	Mortality No	Sensitivity	specificity	Accuracy	PPV	NPV
Positive	42	80	89.3%	73.1%	75.3%	34.4%	97.7%
Negative	5	218					
PSI≥130 point	Mortality Yes	Mortality No	Sensitivity	specificity	Accuracy	PPV	NPV
Positive	32	104	68.0%	65.5%	65.9%	23.5%	92.9%
Negative	15	198					
CURB 65≥3	Mortality Yes	Mortality No	Sensitivity	specificity	Accuracy	PPD	NPD
Positive	38	94	80.8%	68.4%	70.1%	13.6%	95.7%
Negative	7	204					
SII>3551	Mortality Yes	Mortality No	Sensitivity	specificity	Accuracy	PPD	NPD
Positive	30	95	63.8%	68.1%	67.5%	24.0%	92.2%
Negative	17	203					

AUC in terms of 28-day mortality were 0.820 (95% CI: 0.757–0.882; p=0.00), 0.737(95% Cl: 0.672–0.802; p: 0,00), 0.681 (95% CI: 0.604–0.758; p=0.00), and 0.73 (95% Cl: 0.712–0.834; p=0.00), respectively, indicating a strong relation between 28-day mortality LCRP, SII and CURB-65; however, there was a weak association between mortality and PSI (Fig. 1). Bonferroni adjusted p test was performed in the ROC comparison. A statistically significant result was determined (p=0.00). Based on the value of LCRP of 4 for 28-day mortality, we found that the sensitivity, specificity, and accuracy rates were 89.3 %, 73.1 %, and 75.36 %, respectively. Based on the average SII>3551 for predicting 28-day mortality, the sensitivity, specificity, and accuracy rates were 63.8 %, 68.1 % and 67.5 % respectively. Based on the PSI value above 130 points for 28-day mortality, we found that the sensitivity, specificity, and accuracy rates were 68.0 %, 65.5 %, and 65.9%, respectively. With the CURB-65 value of prediction scores as 3 points and above and as a cutoff value for 28-day mortality, we found that the sensitivity, specificity, and accuracy rates were 80.8 %, 68.4 %, and 70.1 %, respectively (Tab. 2). Forty-seven patients died during the first 28-day period. Of these, 42 (89.3%) had LCRP level < 4 (Fisher exact test, p=0,000). Figures 2 and 3 shows the Kaplan–Meier survival curve for LCRP and SII level according to these cutoff values. Patients with LCRP levels below the cutoff value and SII levels above the cutoff values had significantly higher mortality rates than those with LCRP levels above the cutoff and SII levels below the cutoff values at 28-days (log-rank test=25.73, 95% Cl=25.07–26.39; p=0.00). Independent predictors for 28-day mortality rates were determined to be LCRP (<4), SII (>3551), CRP, CURB-65, PSI, age, gender and stay ICU ($p \leq 0.05$) (Tab. 3).

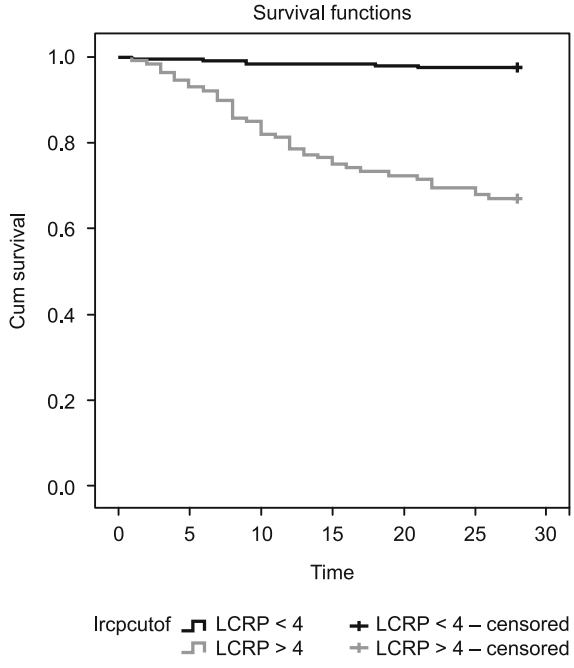

Fig. 2. Kaplan-Meier survival curve according to LCRP level above and below optimal cutoff value (4,00).

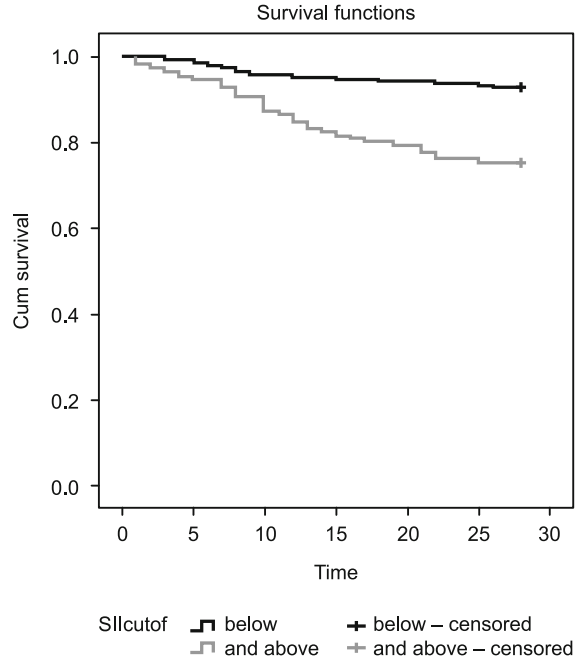

Fig. 3. Kaplan-Meier survival curve according to SII level above and below mean value (3551) for 28-days.

Tab. 3. Multivariate logistic regression analysis for the prediction of death.

Variables for 28 d	Odds ratio	95% CI	P
Age	1.109	1.053–1.167	0.000
Gender	1.854	1.043–3.296	0.035
LCRP	5.199	1.377–19.632	0.015
CRP	1.012	1.010–1.015	0.001
CURB-65	4.290	2.498–7.368	0.000
PSI	3.409	1.913–6.075	0.000
SII	3.732	2.041–6.825	0.000
Stay ICU	1.152	0.983–1.349	0.000

LCRP: Lymphocyte C reactive protein ratio, CURB-65 (Confusion, Urea, Respiratory Rate, Blood pressure, Age> 65 years), PSI: pneumonia severity index, ICU: intensive care unit, SII: Systemic immune-inflammation index

Discussion

We found that pneumonia prediction scores could be strong indicators of 28-day mortality for CAP cases. These results were compatible with those of the previous study. In this study, we used new markers, LCRP and SII, and found that these may also be a strong indicator for 28-day mortality. These markers determined mortality similar to the prediction scores that are presently used widely. To our knowledge, this is the first study to evaluate the relationship between LCRP, SII and mortality in CAP patients and report remarkable results.

We also determined that the in-hospital mortality of CAP patients was 11 %. After further examination in terms of 28-day mortality, this rate increased to 13.6 %. Studying CAP patients who were hospitalized, Akyil et al (12) reported 1-month mortality rates ranging from 8.7–12 %. Other studies on CAP patients reported that 1-year mortality was between 17 % and 45 % (13, 14). For example, Madhu et al (15) reported mortality rate of 18 % in this patient group. Some other studies stated that the mortality rate was around 14 %, but for patients requiring ICU hospitalization, this rate increased to approximately 20–50 % (16–18). In our study, the mortality rate was compatible with the literature; similarly, in-hospital mortality and 28-day mortality were 11 % and 13 %, respectively.

NLR derived from neutrophils and lymphocytes is known to be an inflammatory marker that can increase especially in situations causing inflammation. Many studies have investigated this issue. The increase in neutrophil and lymphopenia, especially in bacterial infections, may be the most important mechanism that demonstrates the power of this marker in detecting bacterial infections (3, 19, 20). Discussing the inflammatory markers in the differentiation of patients with CAP and pulmonary tuberculosis (TBC), Yoon-NB and colleagues stated that NLR could be used as an important marker for CAP and TBC separation, especially when NLR was determined to have a cutoff value of 7. Moreover, the authors stated that NLR is a more important marker in the bacterial CAP diagnosis than WBC, lymphocyte, and CRP (21). The LRCP is a parameter that can be used as an inflammation marker, similar to NLR. This rate occurs, especially in bacterial infections, by dividing the lymphocyte level the amount of which will decrease relatively, with the CRP whose blood value will increase. Its use as an inflammatory marker is extremely novel. In our recent review, few studies that have investigated this ratio have been identified in the literature and works involved cancer patients. At the end of these studies, they reported that the LCRP was an inflammation marker associated with mortality and postoperative management (22, 23). In our study, the statistical significance of this inflammation marker has also been reported. The relationship of the new marker LCRP with mortality is significant enough to be compared with the frequently used prediction scores to determine disease severity and mortality, thus demonstrating the importance of our study.

Similar to other markers, SII can be used as a new marker calculated by the counting's of peripheral blood cells and showing inflammation. In this study it has been shown to be a more objective marker with better predictive reliability for host immune and inflammatory status and prognosis. When the literature is investigated, it is seen that SII is used in several oncological studies (24–26). Our study is the first to evaluate the infection process. When evaluated together with the results, we think that its contribution to the literature will carry importance.

There are many scoring systems that have been used to estimate the prognosis of CAP patients, including CURB-65, PSI, SMART COP, CRB-65, CURB, ATS 2001, SCAP, and ATS/ADSA, to name a few (15, 27). PSI and CURB-65 are also frequently used in our hospital for proper prognosis. These are the prediction scores preferred by physicians in determining the need to provide intensive care for patients and considering their severity in terms of morbidity and mortality (15). Madhu et al (15) reported that PSI and CURB-65 deal with mortality, indicating that when the scoring points increased, the mortality also increased in their study. Marti et al (27) stated that "these two scores (PSI and CURB-65), derived and validated to predict 30-day mortality, perform poorly to predict ICU admission, with an estimated AUC of 0.69" and "PSI and CURB-65 do not have sufficient operating characteristics to be useful for making ICU triage decisions in severe CAP." In accordance with the literature, the results of these scoring systems in our study are directly proportional to 28-day mortality. In other words, as the score points increase, the severity and 28-day mortality of pneumonia increase. Moreover, using LRCP and SII as the determinant of 28-day mortality, we found that it can be as successful as PSI and CURB-65 in providing an accurate estimation of 28-day mortality.

Thus, CAP is still considered an important public health problem due to the severity of the disease and the widespread usage of antibiotics. If it is not treated properly, its mortality can reach 20 %. Fortunately, this rate can be reduced by the early detection and appropriate treatment of serious patients. Finally, LCRP and SII, which are the inflammation markers to be used with the severity scoring systems, can be helpful in determining the mortality of the cases. We believe that early recognition of serious patients with this marker is important for reducing mortality

Limitation

Blood, bronchoalveolar lavage, or sputum cultures were not performed routinely in our ED for patients with CAP. Therefore, it is not clear whether it is caused by a viral or bacterial pathogen. In fact, although the neutrophil, the lymphocyte and CRP ratio are

estimated to be directly related to whether the agent of pneumonia is viral or bacterial, failure to make this distinction may be considered as the most important limitation of this study.

An additional limitation to this study is the exclusion of non-severe CAP patients who were not hospitalized; this weakens the conclusions regarding the negative predictive value of LCRP and SII for mortality

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Received October 27, 2020.
Accepted November 26, 2020.