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Predictive Value of Early Warning Scores for Procalcitonin and CRP in Hospitalized Community-Acquired Pneumonia Patients

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ABSTRACT

Background: Pneumonia is a lower respiratory tract infection that causes the most deaths worldwide. There is a lack of knowledge about the predictive value of Early Warning Score (EWS) for procalcitonin, CRP, Mortality in Community Acquired Pneumonia (CAP).

Purpose: The aim of this study was to see how accurate the EWS is at predicting procalcitonin, CRP and the mortality in Community Acquired Pneumonia patients who are hospitalized. All adult patients who were hospitalized for confirmed CAP between March and June 2023 were retrospectively included.

Methods: A Total of 61 confirmed CAP patients treated in Internal Medicine High Care Unit were included in the present study.

Results: The results showed that EWS≥8 was equivalent to procalcitonin in the septic shock category with (OR: 4.667), while EWS≥7 was equal to high risk CRP with (OR: 5.727), and the risk of mortality (83.3%).

Conclusion: Based on the data analysis test, it concluded that EWS could used as a measuring tool to predict procalcitonin and CRP values, as well as mortality risk.

Keywords: CPR, EWS, procalcitonin

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BACKGROUND

Pneumonia is the most common cause of lower respiratory tract infections which causes the most deaths in the world (Martin-Loeches & Torres, 2021). Pneumonia is a world health problem because it has numbers high mortality, not only in developing countries but also in countries proceed. Pneumonia in America is the 4th cause of death in old age, in Brunei Darussalam 9th, in Malaysia 7th, in Singapore 3rd, and causes 6th death in Thailand (Irawan et al., 2019). As many as 4% of Indonesia's population is diagnosed with pneumonia, and it is the 9th leading cause of death (Riskesdas Ministry of Health of the Republic of Indonesia, 2018).

Patients with severe pneumonia infections are required to be hospitalized with the risk of death due to severe sepsis (Zhou, 2020). The mortality rate that occurs in outpatients is 2%, inpatients are 5-20%, and in intensive care >50% (Purwitasari et al., 2017). Carrying out initial screening of patient severity levels both during outpatient care and hospitalization are effort that must be made to determine the prognosis and appropriate initial therapy (Sungurlu & Balk, 2018a). The earlier it is diagnosed pneumonia, early therapy is carried out immediately to prevent the patient from falling into sepsis conditions (Julián-Jiménez et al., 2017). Therefore, the patient fell In conditions of sepsis, it will become increasingly difficult to treat (Saeed et al., 2019).

Initial screening of pneumonia patients can be done based on symptoms and laboratory biomarker results (Sbiti-Rohr et al., 2016). Initial diagnosis is using PSI (Pneumonia Severity Index) whose results are categorized based on the level of severity and follow-up that must be carried out (Park et al., 2022b). If the patient is suspected of falling into a condition of sepsis then an examination is carried out It is necessary to examine infection biomarkers to determine the spread of infection and therapy (Ranzani et al., 2018). Sepsis biomarker examination often used is procalcitonin or C-Reactive Protein (Tripon et al., 2021). Procalcitonin is a good and effective marker of sepsis to describe the severity of systemic bacterial infections, while C-reactive protein is a predictor that can estimate the cause of infection either due to bacteria or non-bacteria and determine the degree of organ damage due to sepsis (Sungurlu & Balk, 2018).

The observation system carried out in hospitals currently uses the Early Warning Score which contains a score of vital signs and level of consciousness (Sbiti-Rohr et al., 2016). When the patient is hospitalized, vital signs will be monitored using the Early Warning Score periodically, with appropriate periods with the score value, The higher the value of the Early Warning Score the shorter the observation period will be, or in other words it will the more frequently observations are made (Alam et al., 2014). Early Warning Value A high score indicates the patient's prognostic level and follow-up must be done (Sbiti-Rohr et al., 2016).

OBJECTIVE

Based on existing theory It was previously explained that the values of procalcitonin and C-reactive protein were high can describe the severity of the patient's infection, and the Early score Warning Score which describes the patient's prognosis. So, researchers are interested in observing whether there is a correlation between the Early Warning Score values with sepsis biomarkers procalcitonin and C-Reactive Protein in patients with pneumonia treated in Hospital

METHODS

We conducted a retrospective and single-center study. All patients were hospitalized with CAP in Internal Medicine High Care Unit between 1 March and 30 June 2023 included.

Sampling technique with total sampling method. Fit of the entire population sample that meets the inclusion and exclusion criteria. A total of 61 patients were in the present study.

The inclusion criteria for this study were patients hospitalized in the Internal Medicine High Care Unit with a PSI score > 70 and an EWS score ≥ 5. These underwent laboratory tests for procalcitonin and C-Reactive Protein during the hospitalization period. Pneumonia patients who had comorbid autoimmune diseases and were receiving steroid treatment were exclusion criteria in this study.

Data were collected through the Electronic Medical Record (EMR) in the main computer of the Internal Medicine High Care Unit for 2 weeks. There were 5 variables from the EMR in addition of demographic data, including: 1) PSI score data obtained from assessments, diagnoses, or Integrated Patient Progress Notes by doctors. 2) EWS score data is obtained from the EWS column filled in by the nurse. 3) Procalcitonin data is obtained through the clinical pathology column which contains a history of laboratory results. 4) CRP value data is also obtained from the same clinical pathology column as procalcitonin. 5) Data on patients entering and leaving the HCU, obtained from patient registration, medical resumes or Integrated Patient Progress Notes, data obtained also from the nurse's report book which contains records of patients leaving and entering the High Care Unit for internal diseases.

Early warning score contains 7 parameters: Respiration rate, oxygen saturation, supplemental oxygen, temperature, blood pressure, pulse, and level of consciousness (Jones, 2012). The Pneumonia Severity Index contains scores of demographic data, physical examination, and laboratory/radiological results. The results are divided into 5 risk classes (Fine et al., 1997). Procalcitonin is an accurate biomarker for determining bacterial infections of the respiratory tract. Procalcitonin cannot specifically identify the cause of infection, but procalcitonin will increase significantly as pathogenic bacteria increase (Sungurlu & Balk, 2018). Procalcitonin cannot specifically identify the cause of infection, but procalcitonin will increase significantly as pathogenic bacteria increase (Sungurlu & Balk, 2018). Procalcitonin is divided into 5 categories with the most severe category (≥10ng/ml) being sepsis shock. C-Reactive Protein (CRP) is used as a prognostic marker of complications that will occur (Barak-Corren et al., 2021). CRP values are divided into 3 categories : low risk, medium risk, and high risk (Minnaard et al., 2017). This clinical study was approved by the ethics committee of Dr. Soetomo General Teaching Hospital protocol no: 0679/KEPK/V/2023.

We used SPSS (Statistical Package for Social Sciences, SPSS, inc., Chicao, IL, USA) for windows 25.0 program for the statistical analysis. We used kolmogorov-smirnov to evaluate the distribution and homogeneity of variables. To find the level of relationship between variables, use the Pearson correlation test if the data is nominal and the Spearman test if the data is ordinal. Meanwhile, to determine the EWS cutoff point for the risk value of procalcitonin septic shock, high risk value of CRP, and mortality in pneumonia using the ROC (Receiver Operating Characteristics) and AUC (Area Under Curve) tests, to find the Odds Ratio value using the binary logistic regression test. The results were assessed at a 95% confidence interval, with a value of $p<0.05$ considered statistically significant.

RESULTS

There were 61 research samples who met the inclusion criteria. The largest gender was 39 women (63.94%) while 22 men (36.06%). Patient age varied with a mean ± standard deviation of (59.82 ± 13.674). Patient comorbidities consisted of Kidney disease (41%), Gastro-Hepato Disease (8.2%), diabetes mellitus (29.5%), Hematology-Oncology Disease 11.5%, Cerebrovascular disease (8.2%), Sepsis (1.6%).

Table 1. Baseline characteristics of the patients

	Pasien		p
	n	%	
Age (Years)	59,82±13,674		
Gender			
Male	22	36,06	
Female	39	63,94	
Comorbidities			
Kidney Disease	25	41%	
Gastrology-Hepatology Disease	5	8,2%	
Diabetes Mellitus	18	29,5%	
Hematology-Oncology Disease	7	11,5%	
Cerebrovascular disease	5	8,2%	
Sepsis	1	1,6%	
PSI (mean±SD)	120,9±31,521		0,045
PCT (mean±SD)	12,7477±19,10		0,000
CRP (mean±SD)	12,9766±9,4662		0,200
EWS (mean±SD)	6,92±2,894		0,009
LOS (min-max)	(1-27)		0,000

PSI: Pneumonity Severity Index, PCT: Procalcitonin, CRP: C-reactive protein, EWS: Early Warning Score, LOS: Length OF Stay

The results of the data normality test showed that the p-value of PSI was (p=0.045), procalcitonin (p=0.000), CRP (p=0.200), EWS (p=0.009), and length of stay (p=0.000). The patient's length of stay is a minimum of one day and a maximum of 27 days. Mean ± SD values of (PSI = 120 ± 31.521), (PCT = 12.7477 ± 19.10), (CRP = 12.9766 ± 9.4662), and (EWS = 6.92 ± 2.894). Most of the patients' PSI scores were at risk class IV (29) people, while (22) people were at risk class V. Most patients' EWS scores were at high scores (29) people, the procalcitonin value results for most patients were in the septic shock category (21) people, while the highest CRP value was in the high risk category at (29) people (Table 2). The way patients leave the HCU is in several ways, namely going home (6) people, dying (40) people, going home at the request of the patient (2) people, moving to the ICU (1) person. Test the relationship between variables using the Pearson test with interval data scale requirements.

A total of (22) patients were hospitalized for less than (3) days, of these (22) patients died, (20) people died, the rest were forced to return home (1) person and moved (1) person. (21) patients were hospitalized for (4-7) days, (18) patients were hospitalized for more than (7) days. From the data on patients who were discharged from HCU, the median value (5), mode (3) days, standard deviation (5.88), range (26) with a minimum stay of (1) day and a maximum of (27) days, interquartile range (5.5), and variance (34.65).

Table 2. Patient characteristics based on laboratory result categories and clinical scores

PSI			**EWS**			**Procalcitonin**		**CRP**	
Risk Class		n (61)	EWS		n (61)	(ng/mL)	n (61)	Risk (mg/dL)	n (61)
I	0-50		Normal	0-1		Normal (<0,05)		Low <1	10
II	51-70		Low	2-3	10	Local Infection (≥ 0,05 - < 0,5)	9	Intermediate 1-3	22
III	71-90	10	Medium	4-6	22	Infection Sistemic	16	High >3	29

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						(≥ 0,5 - < 2,0)	
IV	91-130	29	High	≥7	29	Severe Septic (≥ 2,0 - < 10)	15
V	131-395	22				Septic Syok (≥ 10)	21

PSI: Pneumonity Severity Index, EWS: Early Warning Score, CRP: C-Reactive Protein

Table 3. Pearson test of EWS with other variables

		PSI	PCT	CRP	LOS
EWS	Pearson Correlation	.518**	.370**	.481**	-0.215
	Sig. (2-tailed)	0.000	0.003	0.000	0.096

EWS: Early Warning Score, PSI: Pneumonity Severity Index, PCT: Procalcitonin, LOS: Length Of Stay

Based on the results of the Pearson test, the Sig (2-tailed) relationship values obtained for the EWS variable with other variables are (EWS-PSI=0.000), (EWS-PCT=0.003), (EWS-CRP=0.000), and (EWS-Length of stay = 0.096), there is a significant relationship if the Sig (2-tailed) value is <0.005, then the relationship value between EWS and other variables has a significantly relationship.

Pearson Correlation (PC) of the relationship between EWS and PSI is (PC: 0.518) which means it has a moderate relationship, the relationship between EWS and procalcitonin is (PC: 0.370) which means both have a weak relationship, while the relationship between EWS and CRP is (PC: 0.481) has a weak relationship. The relationship between EWS and LOS (PC: -0.215) has a weak negative relationship. Then, test EWS as a measuring tool using Receiver Operating Characteristics (ROC).

The EWS score is used as a measuring tool to determine the procalcitonin value which is the target point in the septic shock category because the number of samples in that category is the highest (21) people. The CRP value associated with EWS is CRP in the high risk category because it includes the largest sample (29) of people. The PSI score associated with EWS is in the high risk class category. The high risk class in PSI is a condition where the patient's prognosis value shows a high risk of mortality. Researchers will also relate the EWS value to patient mortality. The number of patients who died in this study was (40). The following are the results of the ROC test with the AUC curve:

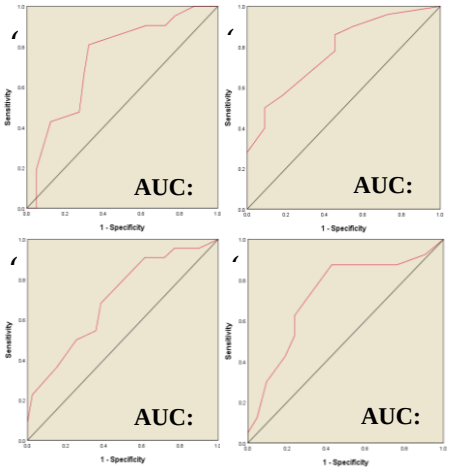

Figure 1: Receiver Operating Characteristic curve analysis of EWS for predicting to (a) Procalcitonin, (b) C-Reactive Protein, (c) Pneumonity Severity Index, (d) Mortality
AUC:Under Curve, CI: Confidence Interval, EWS: Early Warning Score

The results of the ROC analysis test showed that the EWS value was used to predict the septic shock procalcitonin score (AUC: 0.740, p<0.05), C-Reactive Protein (AUC: 0.778, p<0.05), Pneumonia Severity Index (AUC: 0.703 , p<0.05), and Mortality (AUC: 0.726, p<0.05). The cut-off point for the EWS sensitivity and specificity value which is equivalent to procalcitonin for septic shock is ≥8, the cut-off point for the EWS value which is equivalent to high risk CRP is (≥7), the cut-off point for the EWS value which is equivalent to the PSI risk class V score is (≥7) , and patient mortality occurred most frequently in EWS (≥7). After the ROC test, then the binary logistic regression test to determine the Odds Ratio with the following results:

Table 4. Multivariate logistic regression analysis of EWS for predicting procalcitonin, CRP, PSI and Mortality

Realationship between Variables	OR	95% CI		P
		Lower Bound	Upper Bound	
EWS≥8 - Procalcitonin	4,667	1,505	14,469	0,008
EWS≥7 - CRP	5,727	1,121	29,253	0,036
EWS≥7 - PSI	3,429	1,136	10,352	0,029
EWS≥7 - Mortality	5,333	1,621	17,546	0,006

EWS: Early Warning Score, CRP: C-Reactive Protein, PSI: Pneumonity Severity Index, OR: Odds ratio, CI: Confidence Interval

Table 5. PPV, NPV, sensitivity, and specificity of the EWS for predicting procalcitonin, CRP, PSI, and Mortality

Variabel		PPV(%)	NPV(%)	Sen(%)	Spe(%)
EWS≥8	**Procalcitonin**	53,8	80	66,7	70
EWS≥7	**CRP**	93,3	29	56	81,8
EWS≥7	**PSI**	50	77,4	68,2	61,5
EWS≥7	**Mortality**	83,3	51,6	62,5	76,2

EWS: Early Warning Score, CRP: C-Reactive Protein, PSI: Pneumonity Severity Index, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Sen: Sensitivity, Spe: Specificity (Table 4) shows that the OR results of EWS with Procalcitonin were (OR: 4.667. P: 0.008), EWS with CRP (OR: 5.727. P: 0.036), EWS with PSI (OR: 3.429. P: 3.429), and EWS with level Mortality (OR: 5.333. P: 0.006). Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for each variable relationship can be seen that EWS≥8 has a PPV of (53.8%) on procalcitonin for septic shock, while EWS≥7 has a PPV of (93.3%) on CRP high risk, and EWS≥7 has a PPV (50%) on the PSI score class V risk, and EWS≥7 has a PPV (83.3%) on the risk of mortality for pneumonia patients (table 5).

The most common comorbid disease in this study was kidney disease. This can occur due to complications from sepsis pneumonia or already having kidney disease and being exacerbated by pneumonia, because kidney disease has the potential to cause pneumonia (Lubart et al., 2023). Patients with comorbid diabetes mellitus are at risk of developing pneumonia due to decreased immunity and disruption of metabolic processes (Bader et al.,

2016), along with this, blood cortisol increases, triggering hyperglycemia which will worsen the patient's clinical condition (MacIntyre et al., 2012).

Female gender constituted the largest number of patient subjects (39), because women are a group susceptible to pneumonia infections (Huffstetler et al., 2021). The largest age group of patients is more than 60 years old (30), the elderly are an age group that is vulnerable to pneumonia (Corrao et al., 2018). Most of the patients showed symptoms of pneumonia with a moderate risk class PSI score (29), patients with this class risk score began to show several symptoms of organ damage either due to infection or comorbidities they had (Ranzani et al., 2018). The highest mortality rate was in the high risk score, namely 29.2% (Irawan et al., 2019b), but in this study the highest mortality rate was in patients with risk class IV (21) people. Complications from organ damage or comorbidities cause the death rate in the PSI score for this risk class to be high. Even though the largest risk score group was risk class IV (29), the largest positive predictive value was risk class V (83.3%). Patients with a PSI risk class V score show an Early Warning Score (EWS) value equivalent to ≥7 with an Odds ratio (3.429) and p-value (0.029). In this study, the highest procalcitonin value in patients was septic shock (21), (SD=19.10489), patients came in showing symptoms of respiratory infections such as coughing, shortness of breath, fever, and respiratory failure and experienced clinical deterioration alert. In this condition, the procalcitonin value increases (Schuetz et al., 2012), and will decrease if appropriate antibiotic therapy is received (Sungurlu & Balk, 2018). Procalcitonin describes the extent of the spread of infection, so it becomes a consideration when antibiotics should be given (Tamura et al., 2014).

The clinical condition of the high procalcitonin value was measured using the Early Warning Score, patients who were in the septic shock procalcitonin value category were (21) people, based on the results of the relationship test between the EWS value and procalcitonin using the ROC test, the value was obtained (AUC: 0.74), point Cutting sensitivity and specificity, it was found that patients who had septic shock procalcitonin levels (≥10) were equivalent to EWS values ≥8 with values (p=0.008), (OR=4.667) and (PPV=53.8%). This is similar to research conducted by Tamura et al., (2014) that high procalcitonin values reflect the extent of lung inflammation that occurs. EWS≥8 also shows organ damage outcomes equivalent to SOFA values>2 and has a strong relationship to mortality in pneumonia patients, with a mortality rate of (41.1%) (Zhou, 2020). Pneumonia patients who show an EWS score ≥8 are equivalent to the spread of septic shock infection, so it is necessary to administer antibiotics as soon as possible to reduce the level of infection as well as administer supportive drugs to maintain vital signs within normal limits (Ranzani et al., 2018).

As a support for determining the patient's level of infection, an infection biomarker other than procalcitonin is CRP. The CRP value is less sensitive to the level of infection that occurs, however CRP can be used as a marker of organ damage due to infection (Almirall et al., 2004). In this study, there were (29) patients with CRP values >3 (high risk). The EWS value is equivalent to CRP (high risk) based on the ROC test. The value obtained is (AUC: 0.778), the cut point for sensitivity (0.56) and specificity (0.818) is equivalent to EWS=7, with (OR=5.727) (P=0.036) and (PPV=93.3%). These results indicate that EWS≥7 has a high potential for organ damage, although CRP levels are less sensitive to the causes of inflammation that occur (Sungurlu & Balk, 2018) but CRP can still be used as an indicator to measure the possibility of organ damage that occurs, especially when the patient is in a state of sepsis. (Minnaard et al., 2017), therefore, the organ damage that occurs can be identified as originating from sepsis or complications from the patient's comorbid disease (Joffe et al., 2009). Ideally, procalcitonin cannot be separated from CRP in diagnosing possible organ damage due to infection, both of which are used as a guide for starting antibiotic

administration (Bafadhel et al., 2011). This study provides input that an EWS value ≥7 is equivalent to a high risk value from the CRP score. CRP and Procalcitonin both have a significant relationship with EWS values, so to support each other, EWS can be used to measure both in assessing patient prognosis. In this study, 65.6% of (40) patients died. More than 50% of subjects died indicating a high mortality rate from a study (Zhou, 2020). The mortality rate can be predicted based on the patient's clinical condition assessed using EWS (Sbiti-Rohr et al., 2016). Based on the ROC test, it shows that the cut point for sensitivity (0.625) and specificity (0.762) is equivalent to EWS 7. So it can be concluded that EWS≥7 has high mortality, with (OR=5.333) and (PPV=83.3%). The high PPV value of EWS is a consideration for providing appropriate follow-up in order to reduce the risk of death (Jones, 2012). Awareness of a poor prognosis in patients must be done early based on the conclusion of the patient's clinical condition using EWS (Alam et al., 2014).

Knowing the patient's initial clinical condition early will determine appropriate follow-up in order to prevent patient mortality (Fang et al., 2020). The incidence of mortality in patients with EWS ≥7 does not mean that it cannot be prevented, appropriate actions such as providing early emergency treatment, reducing the risk of causes, and administering appropriate medication can be taken immediately so that the EWS score does not increase further and death occurs (Hodgson et al. , 2018). Early treatment is needed in patients with EWS≥7 in order to reduce the risk of mortality and increase patient survival. The combination of the patient's clinical condition using EWS and infection biomarkers (procalcitonin and CRP) in pneumonia patients is a consideration in providing appropriate initial therapy. The earlier the detection is carried out, the better the patient's prognosis will be so that appropriate treatment is carried out to reduce the mortality rate of patients with pneumonia.

CONCLUSION

The results of the current study show that EWS can be used as a measuring tool to predict sepsis biomarkers (procalcitonin and CRP), and the risk of mortality in patients with pneumonia. So high vigilance needs to be exercised in patients with EWS≥7 because it shows a correlation with procalcitonin values for septic shock and a high risk of organ damage (CRP), as well as an increased incidence of mortality in pneumonia patients.

CONFLICT OF INTEREST

There are no conflicts of interest

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