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Submission of Original Research titled "Interleukin-6 Serum Levels's Correlation with Pneumonia Severity Index Scores in Community-Acquired Pneumonia Patient"

Resti Yudhawati <restiyudhawati@gmail.com> Tue, Sep 8, 2020 at 12:17 AM
To: editor.japer@gmail.com

To,
The Editors
Journal of Advanced Pharmacy Education and Research

Dear Sir/Ma'am
We are submitting an Original Research titled "Interleukin-6 Serum Levels's Correlation with Pneumonia Severity Index Scores in Community-Acquired Pneumonia Patient" for consideration for publication in Journal of Advanced Pharmacy Education and Research.

I, Resti Yudhawati, as corresponding author certify that:

* The manuscript is original work of all authors.
* All authors made a significant contribution to this study.
* This manuscript has not been submitted for publication and has not been published in any other journal.
* All authors have read and approved the final version of the manuscript.

Thank you
Sincerely,

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Title Page

Type of article: Original research

Title of the article: Interleukin-6 Serum Levels's Correlation with Pneumonia Severity Index Scores in Community-Acquired Pneumonia Patient

Running title: Interleukin 6 and PSI Score on CAP

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Acknowledgement

We are truly thankful to the patients who participated in the study and the authorities and staff of Dr. Soetomo Hospital, Surabaya, Indonesia, who helped and supported us during the study.

Covering Letter

To,

The Editor

Sub: Submission of Manuscript for publication

Dear Sir,

We intend to publish an article entitled “Interleukin-6 Serum Levels’s Correlation with Pneumonia Severity Index Scores in Community-Acquired Pneumonia Patient” in your esteemed journal as an Original Article/Brief Report.

On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

Prior publication : Nil

Support : Nil.

Conflicts of interest : Authors state there is no conflict of interest.

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We would like to suggest following referees for the article.

Thanking you,

Yours’ sincerely,

Resti Yudhawati

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Abstract

Background

Pro-inflammatory cytokines biomarkers have been extensively assessed for their efficacy in assessment of disease severity. Interleukin-6 (IL-6) with its pleiotropic functions has a potent ability to induce an acute phase of inflammatory responses. This study aims to determine whether there is a correlation between IL-6 level and PSI scores in patients with CAP.

Methods

This study was cross-sectional study. A total of 26 pneumonia patients who met the inclusion and exclusion criteria was included in this study. IL-6 levels and PSI scores were calculated on the first day when the patients treated.

Result

The mean±SD of PSI scores and IL-6 levels were 88.58±25.511 and 161.860±75.0042 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between the level of interleukin-6 and the PSI score with a strong positive correlation r = 0.673 (p-value < 0.05).

Conclusion

IL-6 level and PSI score have a significant and strong positive correlation, these results suggest that IL-6 can be used as a biomarker to determine pneumonia patient's severity.

Keywords: Community-Acquired Pneumonia; Interleukin-6; PSI Scores

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

INTRODUCTION

Pneumonia has a high rate of morbidity and mortality worldwide. Community-Acquired Pneumonia (CAP) leads to 1.3 million persons of care per year and is noted to be the most significant cause of severe sepsis and mortality by infection.[1–3] CAP is a disease that requires serious treatment and can be fatal with the high incidence rate, incidents ranging from 2 to 12 cases per 1,000 population per year and a major cause of mortality from infectious diseases.[4]

People with CAP, assessing the degree of severity in early admission is crucial because it determines the severity of the disease and subsequent treatment.[3, 5, 6] The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V).[7, 9] These scores indicate good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). The management of pneumonia is expected to be better, helping clinicians determine the severity of the disease, determining patient's necessity of hospitalization or ICU care, diagnostic evaluation, determining adequate therapy, and assessment to determine the length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scoring in predicting the outcome of pneumonia sufferers is so doubtful that lately, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their efficacy in the assessment of disease outcomes and severity. Over the past few years, some markers have been tested as a sign of infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes rather than infections.[7, 8]

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Interleukin-6 with its pleiotropic function is associated with pathophysiology of various diseases, therefore the researchers assume will be closely related to the measurement of the pneumonia severity (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, congestive heart disease, kidney disease, cerebrovascular disease), physical examination and laboratory examination. The objective of this study was to determine whether there is a correlation between levels of interleukin-6 with PSI scores in community-acquired pneumonia patients.

METHODS

This research design is an analytic observational with cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, aged over 21 years old, sign informed consent willingly (or represented by the family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Clinically purulent cough with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. On laboratory examination found leukocytosis and on chest x-ray examination there are infiltrates or air bronchogram.

PSI score is a prediction score for assessing the severity of pneumonia consisting of 20 different variables. The total PSI score based on patient characteristics was further classified to determine the risk class to 5 mortality classes (class I – V).

IL-6 examination performed by enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. Measurements of interleukin-6 levels in blood were taken from the patient's

venous blood with a 5 cc syringe, then centrifuged for several minutes, the resulting plasma was taken, then inserted into the tube and stored in the refrigerator with temperature of -70^{o}C. Measurement of interleukin-6 patient serum was performed by the researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Statistical analysis was performed using statistical SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL). Pearson correlation was used to determine the correlation between variables. A p-value of less than 0.05 was considered to be statistically significant.

Ethical clearance

This study follows the principles of the Declaration of Helsinki. Research ethics issued by the ethics committee of Dr. Soetomo Hospital Surabaya (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the study begins.

RESULTS

Demographic Data of Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and the maximum was 86 years old. Most patient were in 51-60 years old group with 9 people (34.60%).

Characteristics of PSI Scores for CAP Patients

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

The high PSI score is mostly due to age, sex and the presence of comorbidities, laboratory tests, and radiological examination of pleural effusion. However, the physical examination did not significantly affect the PSI score because some physical examination results of subjects were still in normal limit (Table 1).

Table 1. Characteristics of PSI Research Subject

Characteristic	Total	Percentage
Male (Age)	18	69.20
Female (Age - 10)	8	30.80
Orphanage/nursing home (+10)	0	0
Comorbid Disease		
Malignancy disease (+30)	8	30.80
Liver disease (+20)	11	42,30
Congestif Heart Disease (+10)	5	19.20
Cerebrovascular Disease (+10)	1	3.80
Renal Disease (+10)	8	30.80
Physical Examination		
Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35˚C or >40˚C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80

BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 of patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD of PSI score was 88.58±25.511. The minimum PSI score was 17 and the maximum was 138 (Table 2).

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels of CAP Patients

In this study, PSI score risk class with most patient was class III (42.3%) then followed by class IV (34.6%). Based on the analysis result, the highest IL-6 level was obtained in PSI class V and the lowest was in class I (Table 3).

Table 3. PSI Score and Mean of IL-6 of CAP Patients

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

Based on the Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Thus, Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and significantly correlated (p-value <0.05) (Table 4).

Table 4. Correlation between Interleukin-6 Level with PSI Score of CAP Patients

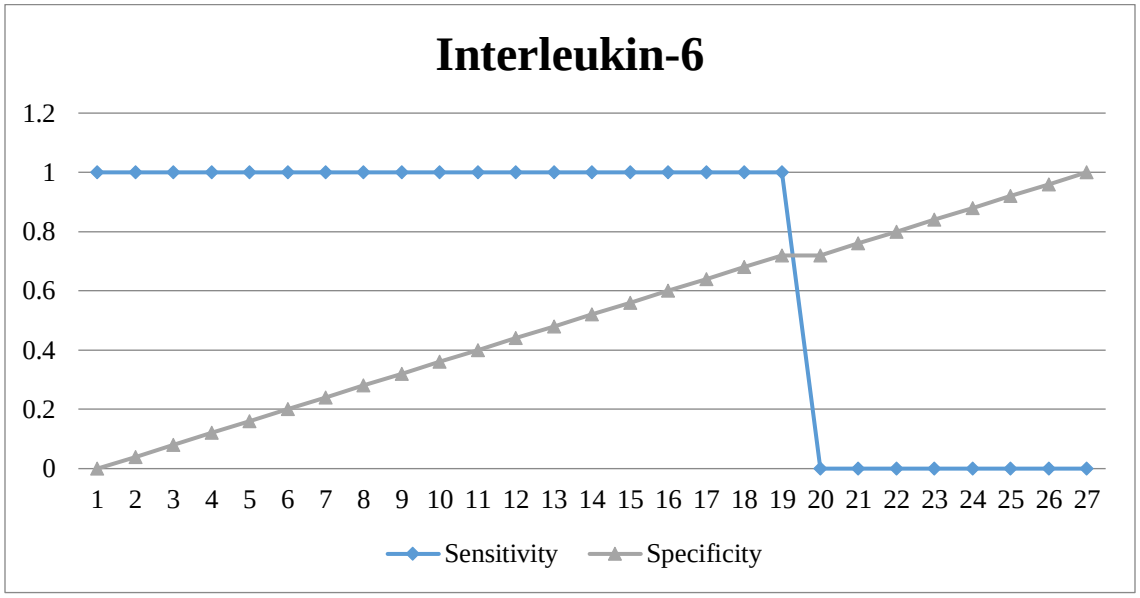
	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of comorbid factors in PSI scores were not calculated, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) (Table 4).

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

IL- 6 cut off point was 184,182 with Area Under Curve (AUC) 28% (95% confidence interval 10.4% -45.6%) with p-value> 0,05. The cutting point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The graph of interleukin-6 AUC is provided in Figure 1.

Figure 1. Graph Area Under Curve Interleukin 6



DISCUSSION

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of the IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum level of IL-6 was 9.92 and the maximum was 106.72. It showed a broad range with serum level was 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in acute phase this interleukin level will increase. Recognition of a microorganism through the interaction between Pattern Recognition Receptors (PRRs) and pathogen-associated molecular patterns (PAMPs).[9] These interactions will activate

various intracellular signal transduction pathways and subsequently activate various transcription factors such as cytosolic nuclear factor-kappa β (NF-kβ). The NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses.[10,11]

The result of this study presented that PSI scores have ranges of values from minimum score of 17 and the maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which is quite significant. Patients who were hospitalized mainly had PSI class of III and IV. This is consistent with the study of Menendez with CAP patients who have a PSI score of class III was 5.6%; class IV was 38.9%; and class V was 55.6%.[12] In line with the research of Ignatio Martin-Loeches, PSI scores of class IV and V were 63.9%.[13] Many pneumonia patients had scores of III and IV mainly because of the age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the lowest in class I. Interleukin-6 levels could determine the prediction of severity, sepsis, and mortality. Likewise with the relation of IL-6 and comorbid diseases, the more comorbid factors appear, the higher the IL-6 level.

Interleukin-6 levels with PSI scores have a strong positive correlation and a significant difference. The result of this research was in line with the report by Stefano et al., which obtained a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05).[14] Otherwise, the result of Menendez research showed there was no significant association between IL-6 and PSI score with p=0.08 (p-value >0.05).[12]

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Interleukin-6 is a multi-functional cytokine that has a significant role in the body defense system, as well as its ability to induce the inflammatory response phase.[15] IL-6 is released by T-cells and macrophages to stimulate the immune response, due to infection, trauma, burns or tissue damage leading to inflammation. High and persistent level of IL-6 are associated with infection and the degree of damage severity. Interleukin-6 with its pleiotropic function is related to the pathophysiology of various diseases, such as metabolic diseases, cancer, liver disease, heart disease, cerebrovascular disease. Interleukin also affects the aging process.[15]

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores.[16] Therefore, IL-6 levels are closely related to PSI scores where comorbid diseases and blood sugar levels also affect interleukin-6. Based on the results above, it can be concluded that the level of IL-6 in patients with community pneumonia are closely related with the patient's PSI score class. The higher the level of IL-6, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization period.[13] Likewise with the study by Menendez et al., IL-6 examination on the first day of hospitalization was closely related to the PSI score class.[12]

In order to know that IL-6 is not affected by comorbid factors or both, the correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. It shows that besides its function to reflects tissue or organ damage, IL-6 levels also can be used to determine the severity of pneumonia if the patient's PSI score is doubtful, where comorbid factor unable to be determined yet.

CONCLUSION

In conclusion, the measurement of IL-6 pro-inflammatory cytokines provides information comparable to the PSI score. Biological markers IL-6 can help clinicians in identifying the severity of pneumonia and increasing the predictive value of mortality to determine the patient's early management to reduce the mortality rate and the length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

Acknowledgement

We are truly thankful to the patients who participated in the study and the authorities and staff of Dr. Soetomo Hospital, Surabaya, Indonesia, who helped and supported us during the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

RY and EY designed the study, collected samples, gathered data, analyzed the data, made tables and figures, wrote the manuscript, and contributed to review and revise. All authors have been approved the final version.

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Original Article

Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia

Resti Yudhawati*, Evi Yuniawati

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia.

Correspondence: Resti Yudhawati, Jalan Jemursari Utara II number 1A, Surabaya, East Java, Indonesia. Phone numbers: +62896-7369-1726. E-mail address: restiyudhawati@gmail.com

ABSTRACT

Background: Biomarkers of pro-inflammatory cytokines have been widely evaluated for their efficacy in assessment of disease severity. Interleukin-6 (IL-6) with its pleiotropic functions has a potent ability to induce the acute phase of inflammatory responses. This aim of this study was to to determine the correlation between IL-6 level and PSI scores in patients with CAP. **Methods**: This study was a cross-sectional study. A total of 26 pneumonia patients who met the inclusion and exclusion criteria were included in this study. IL-6 levels and PSI scores were calculated on the first day of patients treated. **Result**: The mean±SD of PSI scores and IL-6 levels were 88.58±25.511 and 161.860±75.0042 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between interleukin-6 level and PSI score with a strong positive correlation r = 0.673 (p-value < 0.05). **Conclusion**: IL-6 level and PSI score have a significant and strong positive correlation, these results suggest that IL-6 can be used as a biomarker to determine the severity of pneumonia patient.

Keywords: Community-Acquired Pneumonia; Interleukin-6; PSI Scores.

Introduction

Pneumonia has a high morbidity and mortality rate worldwide. Community-Acquired Pneumonia (CAP) affects 1.3 million people annually and is the leading cause of severe sepsis and infection-related mortality[1–3] CAP is a disease that requires serious treatment and can be fatal with a high incidence rate, incidents occur from 2 to 12 cases per 1,000 people per year and are a major cause of mortality from infectious diseases.[4] Health is very important to us [5-8].

In people with CAP, it is very important to assess the severity of early admission because it determines the severity of the disease and subsequent treatment.[3, 9, 10] The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V).[11, 12] These scores represent good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). Pneumonia management is expected to be better, helping clinicians determine the severity of the disease, the need for hospitalization or ICU care, diagnostic evaluation, adequate treatment, and assessment to determine length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scores in predicting the outcome of pneumonia sufferers is so doubtful that recently, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their effectiveness in assessing the outcomes and severity of the disease. Over the past few years, some markers have been tested as for infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes instead of infections.[11, 13]

Interleukin-6 with its pleiotropic function is associated with pathophysiology of various diseases, so researchers assume will be closely related to the measuring the severity of pneumonia (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, congestive heart disease,

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Resti Yudhawati, Evi Yuniawati. Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia. J Adv Pharm Edu Res 2020;10(2):1-6. Source of Support: Nil, Conflict of Interest: None declared.

kidney disease, cerebrovascular disease), physical examination and laboratory examination. The objective of this study was to determine whether there is a correlation between interleukin-6 levels and PSI scores in community-acquired pneumonia patients.

Methods

This research design is an analytic observational with a cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, over 21 years of age, signed informed consent willingly (or indicated by family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Purulent cough is clinically associated with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. Leukocytosis is found on a laboratory examination,and and there is an infiltrating chest or air bronchogram on a chest x-ray.

The PSI score is a predictive score for assessing the severity of pneumonia that consist of 20 different variables. The total PSI score was classified into 5 mortality classes (class I - V) based on the patient characteristics profile to determine the risk class..

IL-6 examination was performed using enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. The measurements of interleukin-6 levels in the blood was taken from the patient's venous blood with a 5 cc syringe, then centrifuged for several minutes, the resulting plasma was obtained, then placed in a tube and stored in a refrigerator at -70°C. Measurement of interleukin-6 patient serum was performed by researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Statistical analysis was performed using SPSS software package for windows, version 17.0 (SPSS, Inc., Chicago, IL). Pearson correlation was used to determine the correlation between variables. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance

This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

Results

Demographic Data of the Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and a maximum of 86 years. Most patient were in the age group of 51-60 years with 9 patients (34.60%).

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Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35°C or >40°C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80
BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 in patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD score of PSI was 88.58±25.511. The minimum PSI score was 17 and the maximum score was 138 (Table 2).

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels in CAP Patients

In this study, the risk class was PSI score in most patients class III (42.3%) and then followed by class IV (34.6%). Based on the analysis result, the highest level of IL-6 was obtained in PSI class V and the lowest was in class I (Table 3).

Table 3. PSI Score and Mean of IL-6 in CAP Patients

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

According to Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Therefore, Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and a significantly correlated (p-value <0.05) (Table 4).

Table 4. Correlation between Interleukin-6 Level and PSI Score of CAP Patients

	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of the comorbid factors were not calculated in the PSI scores, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) (Table 4).

IL- 6 had a cut-off point of 184,182 with Area Under Curve (AUC) of 28% (95% confidence interval 10.4% -45.6%) with a p-value> 0.05. The cut-off point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The interleukin-6 AUC graph is shown in Figure 1.

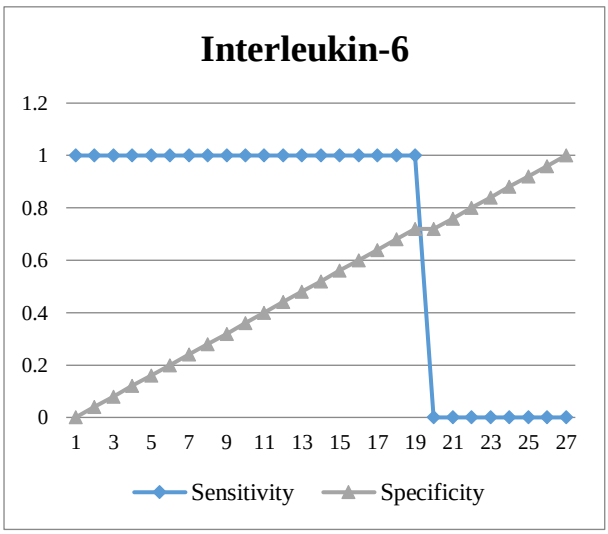

Figure 1. Graph Area Under Curve Interleukin 6

Discussion

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum IL-6 level was 9.92 and the maximum was 106.72. This showed a wide range with a serum level of 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in the cute phase this level of interleukin increases. Recognition of a microorganism through the interaction between Pattern Recognition Receptors (PRRs) and pathogen-associated molecular patterns (PAMPs).[12] These interactions activate various intracellular signal transduction pathways and subsequently activate a variety of transcription factors such as the cytosolic nuclear factor-kappa β (NF-kβ). NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region, and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses.[14, 15]

The results of this study showed that PSI scores have ranges of values from minimum score of 17 and maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which is quite significant. Patients who were hospitalized mainly had PSI class III and IV. This is consistent with the Menendez study of CAP patients with a class III PSI score of 5.6%; class IV was 38.9%; and class V was 55.6%.[16] According to research by Ignatio Martin-Loeches, PSI scores in class IV and V were 63.9%.[17] Many pneumonia patients had scores of III and IV mainly because of the age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the lowest in class I. Interleukin-6 levels can predict severity, sepsis, and mortality. Similarly, with the relation of IL-6 and comorbid

diseases, the more comorbid factors appear, the higher the level of IL-6..

Interleukin-6 levels were positively correlated with PSI scores and was a significant difference. The result of this study were in accordance with the report of Stefano et al., which showed a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05).[18] Otherwise, the result of Menendez study showed that there was no significant association between IL-6 and PSI score with p=0.08 (p-value >0.05).[16]

Interleukin-6 is a multi-functional cytokine that plays a significant role in the body's defense system, as well as its ability to induce the inflammatory response phase.[19] IL-6 is released by T-cells and macrophages due to stimulate the immune response, infection, trauma, burns or tissue damage leading to inflammation. High and persistent level of IL-6 are associated with infection and severity of injury . Interleukin-6 with its pleiotropic function is related to the pathophysiology of various diseases, such as metabolic diseases, cancer, liver disease, heart disease, cerebrovascular disease. Interleukin also affects the aging process.[19]

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores.[20] Therefore, IL-6 levels are closely related to PSI scores in which comorbid diseases and blood sugar levels also affect interleukin-6. According to the above results,, it can be concluded that the level of IL-6 in patients with community pneumonia is closely related to the patient's PSI score class. The higher the IL-6 level, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization period.[17] Similarly, according to Menendez et al., IL-6 examination on the first day of hospitalization was closely related to the PSI score class.[16]

In order to know that IL-6 is not affected by comorbid factors or both, correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. This suggests that in addition to its function to reflects tissue or organ damage, IL-6 levels also can be used to determine the severity of pneumonia if the patient's PSI score is doubtful, where comorbid factor unable to be determined yet.

Conclusion

In conclusion, measurement of IL-6 pro-inflammatory cytokines provides information comparable to PSI score. IL-6 Biological markers can help clinicians in identifying the severity of pneumonia and increase the predictive value of mortality to determine early patientmanagement to reduce mortality rate and length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

Acknowledgement

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Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

RY and EY designed the study, collected samples, gathered data, analyzed the data, made tables and figures, wrote the manuscript, and contributed to review and revise. All authors have been approved the final version.

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Resti Yudhawati <restiyudhawati@gmail.com>
to Japer

Sun, Sep 20, 2020, 12:16 AM

Dear Editor,

Thank you very much for revising our manuscript, especially the language and grammar, we really appreciate it. However, after we checked it, we found some corrections. We highlighted it as blue and yellow, also we inserted some comments. We could not agree with the addition of a sentence and addition of the references, because they do not correlate with the topic of our manuscript. Please kindly check the attached file below and inform us after you revise it. Thank you very much for your help.

Best regards,
Resti Yudhawati

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Original Article

Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia

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ABSTRACT

Background: Biomarkers of pro-inflammatory cytokines have been widely evaluated for their efficacy in assessment of disease severity. Interleukin-6 (IL-6) with its pleiotropic functions has a potent ability to induce the acute phase of inflammatory responses. This aim of this study was to to determine the correlation between IL-6 level and PSI scores in patients with CAP. **Methods**: This study was a cross-sectional study. A total of 26 pneumonia patients who met the inclusion and exclusion criteria were included in this study. IL-6 levels and PSI scores were calculated on the first day of patients treated. **Result**: The mean±SD of PSI scores and IL-6 levels were 88.58±25.511 and 161.860±75.0042 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between interleukin-6 level and PSI score with a strong positive correlation r = 0.673 (p-value < 0.05). **Conclusion**: IL-6 level and PSI score have a significant and strong positive correlation, these results suggest that IL-6 can be used as a biomarker to determine the severity of pneumonia patient.

Keywords: Community-Acquired Pneumonia; Interleukin-6; PSI Scores.

Introduction

Pneumonia has a high morbidity and mortality rate worldwide. Community-Acquired Pneumonia (CAP) affects 1.3 million people annually and is the leading cause of severe sepsis and infection-related mortality[1–3] CAP is a disease that requires serious treatment and can be fatal with a high incidence rate, incidents occur from 2 to 12 cases per 1,000 people per year and are a major cause of mortality from infectious diseases.[4] ~~Health is very important to us~~ [5–8].

In people with CAP, it is very important to assess the severity of early admission because it determines the severity of the disease and subsequent treatment.[3, 9, 10] The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V).[11, 12] These scores represent good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). Pneumonia management is expected to be better, helping clinicians determine the severity of the disease, the need for hospitalization or ICU care, diagnostic evaluation, adequate treatment, and assessment to determine length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scores in predicting the outcome of pneumonia sufferers is so doubtful that recently, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their effectiveness in assessing the outcomes and severity of the disease. Over the past few years, some markers have been tested as for infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes instead of infections.[11, 13]

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Resti Yudhawati, Evi Yuniawati. Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia. J Adv Pharm Edu Res 2020;10(2):1-6. Source of Support: Nil, Conflict of Interest: None declared.

Interleukin-6 with its pleiotropic function is associated with pathophysiology of various diseases, so researchers assume will be closely related to the measuring the severity of pneumonia (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, congestive heart disease, kidney disease, cerebrovascular disease), physical examination and laboratory examination. The objective of this study was to determine whether there is a correlation between interleukin-6 levels and PSI scores in community-acquired pneumonia patients.

Methods

This research design is an analytic observational with a cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, over 21 years of age, signed informed consent willingly (or indicated by family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Purulent cough is clinically associated with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. Leukocytosis is found on a laboratory examination,and ~~and there is an infiltrating chest or air bronchogram on a chest x-ray~~.

The PSI score is a predictive score for assessing the severity of pneumonia that consist of 20 different variables. The total PSI score was classified into 5 mortality classes (class I - V) based on the patient characteristics profile to determine the risk class.

IL-6 examination was performed using enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. The measurements of interleukin-6 levels in the blood was taken from the patient's venous blood with a 5 cc syringe, then centrifuged for several minutes, the resulting plasma was obtained, then placed in a tube and stored in a refrigerator at -70°C. Measurement of interleukin-6 patient serum was performed by researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Statistical analysis was performed using SPSS software package for windows, version 17.0 (SPSS, Inc., Chicago, IL). Pearson correlation was used to determine the correlation between variables. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance

This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

Results

Demographic Data of the Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and a maximum of 86 years. Most patient were in the age group of 51-60 years with 9 patients (34.60%).

Characteristics of PSI Scores for CAP Patients

The high PSI score is mostly due to age, sex and the presence of comorbidities, laboratory tests, and radiological examination of the pleural effusion. However, physical examination did not significantly affect the PSI score because some of the physical examination results were still in normal limit (Table 1).

Table 1. Characteristics of PSI Research Subject

Characteristic	Total	Percentage
Male (Age)	18	69.20
Female (Age - 10)	8	30.80
Orphanage/nursing home (+10)	0	0
Comorbid Disease		
Malignancy disease (+30)	8	30.80
Liver disease (+20)	11	42,30
Congestif Heart Disease (+10)	5	19.20
Cerebrovascular Disease (+10)	1	3.80
Renal Disease (+10)	8	30.80
Physical Examination		
Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35°C or >40°C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80
BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 in patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD score of PSI was 88.58±25.511. The minimum PSI score was 17 and the maximum score was 138 (Table 2).

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels in CAP Patients

In this study, the risk class was PSI score in most patients class III (42.3%) and then followed by class IV (34.6%). Based on the analysis result, the highest level of IL-6 was obtained in PSI class V and the lowest was in class I (Table 3).

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PSI Score Class	Total	Mean±SD	Minimum	Maximum
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The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

According to Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Therefore, Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and a significantly correlated (p-value <0.05) (Table 4).

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	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
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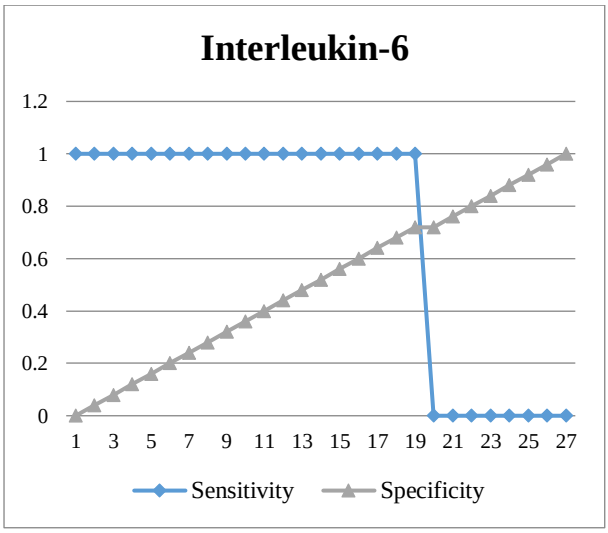

Figure 1. Graph Area Under Curve Interleukin 6

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Conflict of interest

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Author's contribution

RY and EY designed the study, collected samples, gathered data, analyzed the data, made tables and figures, wrote the manuscript, and contributed to review and revise. All authors have been approved the final version.

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Original Article

Correlation of Serum Interleukin-6 level and Pneumonia Severity Index Score in Patient with Community-Acquired Pneumonia

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ABSTRACT

Biomarkers of pro-inflammatory cytokines have been widely evaluated for their efficacy in the assessment of disease severity. The pleiotropic functions of Interleukin-6 (IL-6) allow it to induce the inflammatory responses acute phase. This study aimed to evaluate the correlation between PSI scores in patients with CAP and IL-6 levels. The study was a cross-sectional study. 26 pneumonia patients who met the inclusion and exclusion criteria were included in this study. IL-6 levels and PSI scores were calculated on the first day of patients treated.

The mean±SD of PSI scores and IL-6 levels were 161.860±75.0042 and 88.58±25.511 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between the PSI score and interleukin-6 level with a strong positive correlation r = 0.673 (p-value < 0.05). PSI score and IL-6 level have a strong and significant positive correlation, these results suggest that IL-6 can be used as a biomarker to determine the severity of pneumonia inpatient.

Keywords: Community-Acquired Pneumonia, Interleukin-6, PSI Scores, Disease severity

Introduction

Globally, Pneumonia has a high mortality and morbidity rate. Community-Acquired Pneumonia (CAP) affects 1.3 million people annually and is the leading cause of severe sepsis and infection-related mortality [1-3]. CAP is a disease that requires serious treatment and can be fatal with a high incidence rate, incidents occur from 2 to 12 cases per 1,000 people per year and are the main factors of mortality from infectious diseases [4].

In people with CAP, it is very important to assess the severity of early admission because it determines the severity of the disease and subsequent treatment [3, 5, 6]. The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V) [7, 8]. These scores represent good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). Pneumonia management is expected to be better, helping clinicians determine the disease severity, the need for hospitalization or ICU care, diagnostic evaluation, adequate treatment, and assessment to determine the length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scores in predicting the outcome of pneumonia sufferers is so doubtful that recently, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their effectiveness in assessing the outcomes and severity of the disease. Over the past few years, some markers have been tested for infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes instead of infections [7, 9].

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How to cite this article: Yudhawati R, Yuniawati E. Correlation of serum Interleukin-6 level and Pneumonia severity index score in a patient with community-acquired Pneumonia. J Adv Pharm Edu Res. 2021;11(2):xx-xx. https://doi.org/

Interleukin-6 with its pleiotropic function is related with the various diseases' pathophysiology, so researchers assume will be closely related to measuring the severity of pneumonia (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, physical examination, kidney disease, cerebrovascular disease), congestive heart disease and laboratory examination. The objective of this study was to evaluate whether there is a correlation between PSI scores and interleukin-6 levels in community-acquired pneumonia patients.

Materials and Methods

This research design is an analytic observational with a cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, over 21 years of age, signed informed consent willingly (or indicated by family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Purulent cough is clinically associated with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. Leukocytosis is found on a laboratory examination, and there is a pulmonary infiltrate or air bronchogram on a chest x-ray.

The PSI score is a predictive score for assessing the severity of pneumonia that consists of 20 different variables. The total PSI score was classified into 5 mortality classes (class I - V) based on the patient characteristics profile to determine the risk class.

IL-6 examination was performed using the enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. The measurements of interleukin-6 levels in the blood were taken from the patient's venous blood with a 5-cc syringe, then centrifuged for several minutes, the resulting plasma was obtained, then placed in a tube and stored in a refrigerator at -70°C. Measurement of interleukin-6 patient serum was performed by researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Using the SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL), Statistical analysis was performed. The correlation between variables was evaluated Pearson correlation. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance

This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

Results and Discussion

Demographic Data of the Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and a maximum of 86 years. Most patients were in the age group of 51-60 years with 9 patients (34.60%).

Characteristics of PSI Scores for CAP Patients

The high PSI score is mostly due to age, sex, and the presence of comorbidities, laboratory tests, and radiological examination of the pleural effusion. However, the physical examination did not significantly affect the PSI score because some of the physical examination results were still within the normal limit **(Table 1)**.

Table 1. Characteristics of PSI Research Subject

Characteristic	Total	Percentage
Male (Age)	18	69.20
Female (Age - 10)	8	30.80
Orphanage/nursing home (+10)	0	0
Comorbid Disease		
Malignancy disease (+30)	8	30.80
Liver disease (+20)	11	42,30
Congestif Heart Disease (+10)	5	19.20
Cerebrovascular Disease (+10)	1	3.80
Renal Disease (+10)	8	30.80
Physical Examination		
Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35°C or >40°C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80
BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 in patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD of PSI score was 88.58±25.511. The minimum PSI score was 17 and the maximum score was 138 **(Table 2)**.

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels in CAP Patients

In this study, the risk class was PSI score in most patients class III (42.3%) and then followed by class IV (34.6%). Based on the analysis result, the highest level of IL-6 was obtained in PSI class V and the lowest was in class I **(Table 3)**.

Table 3. PSI Score and Mean of IL-6 in CAP Patients

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

According to the Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Therefore, the Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and a significantly correlated (p-value <0.05) **(Table 4)**.

Table 4. Correlation between Interleukin-6 Level and PSI Score of CAP Patients

	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of the comorbid factors were not calculated in the PSI scores, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) **(Table 4)**.

IL- 6 had a cut-off point of 184,182 with Area Under Curve (AUC) of 28% (95% confidence interval 10.4% -45.6%) with a p-value> 0.05. The cut-off point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The interleukin-6 AUC graph is shown in **Figure 1**.

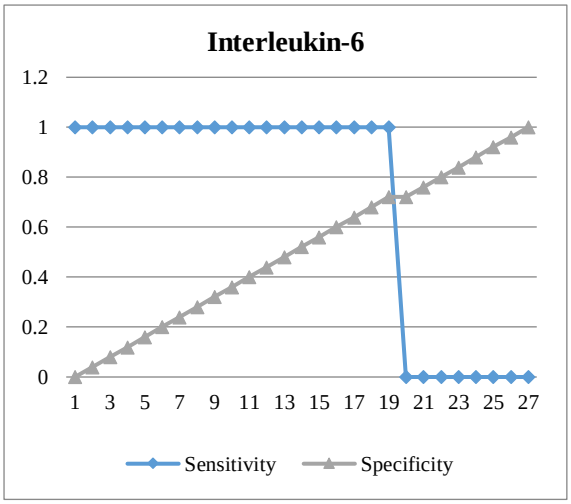

Figure 1. Graph Area Under Curve Interleukin 6

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum IL-6 level was 9.92 and the maximum was 106.72. This showed a wide range with a serum level of 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in the cute phase this level of interleukin increases. Recognition of a microorganism through the interaction between pathogen-associated molecular patterns (PAMPs) and Pattern Recognition Receptors (PRRs) [8]. These interactions activate various intracellular signal transduction pathways and subsequently activate a variety of transcription factors such as the cytosolic nuclear factor-kappa β (NF-kβ). NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region, and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses [10, 11].

The results of this study showed that PSI scores have ranges of values from a minimum score of 17 and a maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which are quite significant. Patients who were hospitalized mainly had PSI class III and IV. This is consistent with the Menendez study of CAP patients with a class III PSI score of 5.6%; class IV was 38.9%, and class V was 55.6% [12]. According to research by

Ignatio Martin-Loeches, PSI scores in class IV and V were 63.9% [13]. Many pneumonia patients had scores of III and IV mainly because of age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the lowest in class I. Interleukin-6 levels can predict severity, sepsis, and mortality. Similarly, with the relation of IL-6 and comorbid diseases, the more comorbid factors appear, the higher the level of IL-6.

Interleukin-6 levels were positively correlated with PSI scores and were a significant difference. The result of this study was in accordance with the report of Stefano *et al.*, which showed a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05) [14]. Otherwise, the result of the Menendez study showed that there was no significant association between IL-6 and PSI score with p=0.08 (p-value >0.05) [12].

Interleukin-6 is a multi-functional cytokine that plays a significant role in the body's defense system, as well as its ability to induce the inflammatory response phase [15]. Due to stimulating the immune response, trauma, burns, infection, or tissue damage leading to inflammation, IL-6 is released by T-cells and macrophages. High and persistent levels of IL-6 are associated with infection and the severity of the injury. Interleukin-6 with its pleiotropic function is related to the various diseases' pathophysiology, such as metabolic diseases, cancer, liver disease, heart disease, cerebrovascular disease. Interleukin also affects the aging process [15].

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores [5]. Therefore, IL-6 levels are closely related to PSI scores in which comorbid diseases and blood sugar levels also affect interleukin-6. According to the above results, it can be concluded that the level of IL-6 in patients with community pneumonia is closely related to the patient's PSI score class. The higher the IL-6 level, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization periods [13]. Similarly, according to Menendez *et al.*, IL-6 examination on the first day of hospitalization was closely related to the PSI score class [12].

To know that IL-6 is not affected by comorbid factors or both, the correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. This suggests that in addition to its function to reflects tissue or organ damage, IL-6 levels also can be used to evaluate pneumonia severity if the patient's PSI score is doubtful, where comorbid factors unable to be determined yet.

Conclusion

In conclusion, measurement of IL-6 pro-inflammatory cytokines provides information comparable to PSI score. IL-6 Biological markers can help clinicians in identifying the severity of pneumonia and increase the predictive value of mortality to determine early patient management to reduce mortality rate and length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

Acknowledgments: We truly thank the patients who participated in this study and the authorities and staff of Dr. Soetomo Hospital, Surabaya, Indonesia, who helped and supported us during the study.

Conflict of interest: None

Financial support: None

Ethics statement: None

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Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Abstract

Background

Pro-inflammatory cytokines biomarkers have been extensively assessed for their efficacy in assessment of disease severity. Interleukin-6 (IL-6) with its pleiotropic functions has a potent ability to induce an acute phase of inflammatory responses. This study aims to determine whether there is a correlation between IL-6 level and PSI scores in patients with CAP.

Methods

This study was cross-sectional study. A total of 26 pneumonia patients who met the inclusion and exclusion criteria was included in this study. IL-6 levels and PSI scores were calculated on the first day when the patients treated.

Result

The mean±SD of PSI scores and IL-6 levels were 88.58±25.511 and 161.860±75.0042 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between the level of interleukin-6 and the PSI score with a strong positive correlation r = 0.673 (p-value < 0.05).

Conclusion

IL-6 level and PSI score have a significant and strong positive correlation, these results suggest that IL-6 can be used as a biomarker to determine pneumonia patient's severity.

Keywords: Community-Acquired Pneumonia; Interleukin-6; PSI Scores

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

INTRODUCTION

Pneumonia has a high rate of morbidity and mortality worldwide. Community-Acquired Pneumonia (CAP) leads to 1.3 million persons of care per year and is noted to be the most significant cause of severe sepsis and mortality by infection.[1–3] CAP is a disease that requires serious treatment and can be fatal with the high incidence rate, incidents ranging from 2 to 12 cases per 1,000 population per year and a major cause of mortality from infectious diseases.[4]

People with CAP, assessing the degree of severity in early admission is crucial because it determines the severity of the disease and subsequent treatment.[3, 5, 6] The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V).[7, 8] These scores indicate good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). The management of pneumonia is expected to be better, helping clinicians determine the severity of the disease, determining patient's necessity of hospitalization or ICU care, diagnostic evaluation, determining adequate therapy, and assessment to determine the length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scoring in predicting the outcome of pneumonia sufferers is so doubtful that lately, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their efficacy in the assessment of disease outcomes and severity. Over the past few years, some markers have been tested as a sign of infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes rather than infections.[7, 9]

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Interleukin-6 with its pleiotropic function is associated with pathophysiology of various diseases, therefore the researchers assume will be closely related to the measurement of the pneumonia severity (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, congestive heart disease, kidney disease, cerebrovascular disease), physical examination and laboratory examination. The objective of this study was to determine whether there is a correlation between levels of interleukin-6 with PSI scores in community-acquired pneumonia patients.

METHODS

This research design is an analytic observational with cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, aged over 21 years old, sign informed consent willingly (or represented by the family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Clinically purulent cough with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. On laboratory examination found leukocytosis and on chest x-ray examination there are infiltrates or air bronchogram.

PSI score is a prediction score for assessing the severity of pneumonia consisting of 20 different variables. The total PSI score based on patient characteristics was further classified to determine the risk class to 5 mortality classes (class I – V).

IL-6 examination performed by enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. Measurements of interleukin-6 levels in blood were taken from the patient's

venous blood with a 5 cc syringe, then centrifuged for several minutes, the resulting plasma was taken, then inserted into the tube and stored in the refrigerator with temperature of -70^{o}C. Measurement of interleukin-6 patient serum was performed by the researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Statistical analysis was performed using statistical SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL). Pearson correlation was used to determine the correlation between variables. A p-value of less than 0.05 was considered to be statistically significant.

Ethical clearance

This study follows the principles of the Declaration of Helsinki. Research ethics issued by the ethics committee of Dr. Soetomo Hospital Surabaya (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the study begins.

RESULTS

Demographic Data of Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and the maximum was 86 years old. Most patient were in 51-60 years old group with 9 people (34.60%).

Characteristics of PSI Scores for CAP Patients

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

The high PSI score is mostly due to age, sex and the presence of comorbidities, laboratory tests, and radiological examination of pleural effusion. However, the physical examination did not significantly affect the PSI score because some physical examination results of subjects were still in normal limit (Table 1).

Table 1. Characteristics of PSI Research Subject

Characteristic	Total	Percentage
Male (Age)	18	69.20
Female (Age - 10)	8	30.80
Orphanage/nursing home (+10)	0	0
Comorbid Disease		
Malignancy disease (+30)	8	30.80
Liver disease (+20)	11	42,30
Congestif Heart Disease (+10)	5	19.20
Cerebrovascular Disease (+10)	1	3.80
Renal Disease (+10)	8	30.80
Physical Examination		
Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35˚C or >40˚C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80

BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 of patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD of PSI score was 88.58±25.511. The minimum PSI score was 17 and the maximum was 138 (Table 2).

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels of CAP Patients

In this study, PSI score risk class with most patient was class III (42.3%) then followed by class IV (34.6%). Based on the analysis result, the highest IL-6 level was obtained in PSI class V and the lowest was in class I (Table 3).

Table 3. PSI Score and Mean of IL-6 of CAP Patients

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

Based on the Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Thus, Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and significantly correlated (p-value <0.05) (Table 4).

Table 4. Correlation between Interleukin-6 Level with PSI Score of CAP Patients

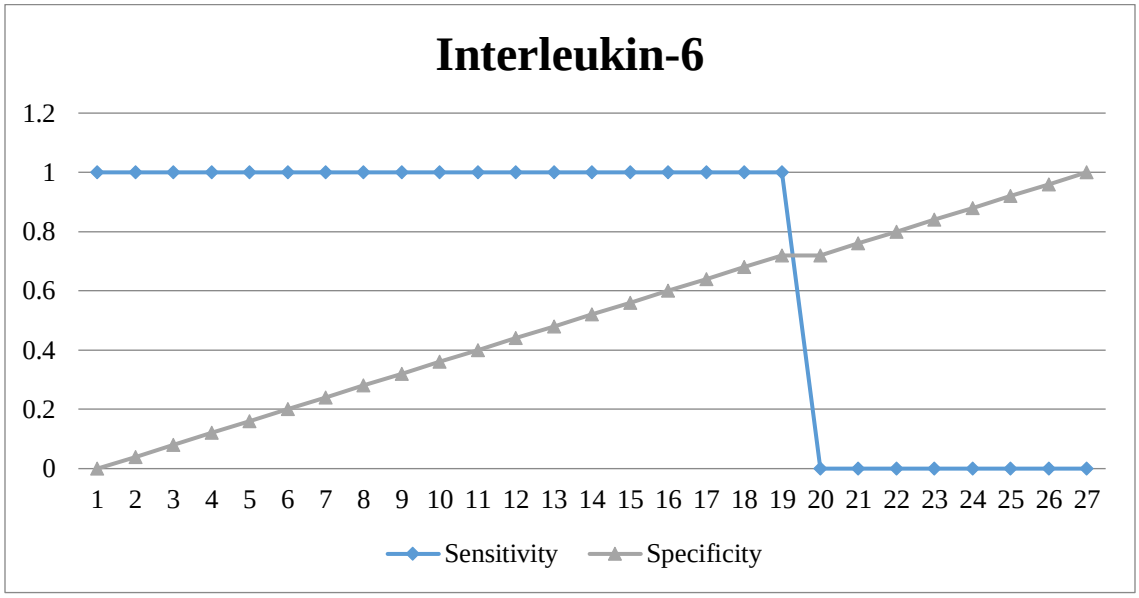
	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of comorbid factors in PSI scores were not calculated, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) (Table 4).

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

IL- 6 cut off point was 184,182 with Area Under Curve (AUC) 28% (95% confidence interval 10.4% -45.6%) with p-value> 0,05. The cutting point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The graph of interleukin-6 AUC is provided in Figure 1.

Figure 1. Graph Area Under Curve Interleukin 6



DISCUSSION

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of the IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum level of IL-6 was 9.92 and the maximum was 106.72. It showed a broad range with serum level was 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in acute phase this interleukin level will increase. Recognition of a microorganism through the interaction between Pattern Recognition Receptors (PRRs) and pathogen-associated molecular patterns (PAMPs).[9] These interactions will activate

various intracellular signal transduction pathways and subsequently activate various transcription factors such as cytosolic nuclear factor-kappa β (NF-kβ). The NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses.[10,11]

The result of this study presented that PSI scores have ranges of values from minimum score of 17 and the maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which is quite significant. Patients who were hospitalized mainly had PSI class of III and IV. This is consistent with the study of Menendez with CAP patients who have a PSI score of class III was 5.6%; class IV was 38.9%; and class V was 55.6%.[12] In line with the research of Ignatio Martin-Loeches, PSI scores of class IV and V were 63.9%.[13] Many pneumonia patients had scores of III and IV mainly because of the age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the lowest in class I. Interleukin-6 levels could determine the prediction of severity, sepsis, and mortality. Likewise with the relation of IL-6 and comorbid diseases, the more comorbid factors appear, the higher the IL-6 level.

Interleukin-6 levels with PSI scores have a strong positive correlation and a significant difference. The result of this research was in line with the report by Stefano et al., which obtained a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05).[14] Otherwise, the result of Menendez research showed there was no significant association between IL-6 and PSI score with p=0.08 (p-value >0.05).[12]

Interleukin-6 Serum Level's Correlation with Pneumonia Severity Index Score in Community-Acquired Pneumonia Patient

Interleukin-6 is a multi-functional cytokine that has a significant role in the body defense system, as well as its ability to induce the inflammatory response phase.[15] IL-6 is released by T-cells and macrophages to stimulate the immune response, due to infection, trauma, burns or tissue damage leading to inflammation. High and persistent level of IL-6 are associated with infection and the degree of damage severity. Interleukin-6 with its pleiotropic function is related to the pathophysiology of various diseases, such as metabolic diseases, cancer, liver disease, heart disease, cerebrovascular disease. Interleukin also affects the aging process.[15]

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores.[16] Therefore, IL-6 levels are closely related to PSI scores where comorbid diseases and blood sugar levels also affect interleukin-6. Based on the results above, it can be concluded that the level of IL-6 in patients with community pneumonia are closely related with the patient's PSI score class. The higher the level of IL-6, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization period.[13] Likewise with the study by Menendez et al., IL-6 examination on the first day of hospitalization was closely related to the PSI score class.[12]

In order to know that IL-6 is not affected by comorbid factors or both, the correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. It shows that besides its function to reflects tissue or organ damage, IL-6 levels also can be used to determine the severity of pneumonia if the patient's PSI score is doubtful, where comorbid factor unable to be determined yet.

CONCLUSION

In conclusion, the measurement of IL-6 pro-inflammatory cytokines provides information comparable to the PSI score. Biological markers IL-6 can help clinicians in identifying the severity of pneumonia and increasing the predictive value of mortality to determine the patient's early management to reduce the mortality rate and the length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

Acknowledgement

We are truly thankful to the patients who participated in the study and the authorities and staff of Dr. Soetomo Hospital, Surabaya, Indonesia, who helped and supported us during the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Author's contribution

RY and EY designed the study, collected samples, gathered data, analyzed the data, made tables and figures, wrote the manuscript, and contributed to review and revise. All authors have been approved the final version.

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Original Article

Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia

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ABSTRACT

Background: Biomarkers of pro-inflammatory cytokines have been widely evaluated for their efficacy in assessment of disease severity. Interleukin-6 (IL-6) with its pleiotropic functions has a potent ability to induce the acute phase of inflammatory responses. This aim of this study was to to determine the correlation between IL-6 level and PSI scores in patients with CAP. **Methods**: This study was a cross-sectional study. A total of 26 pneumonia patients who met the inclusion and exclusion criteria were included in this study. IL-6 levels and PSI scores were calculated on the first day of patients treated. **Result**: The mean±SD of PSI scores and IL-6 levels were 88.58±25.511 and 161.860±75.0042 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between interleukin-6 level and PSI score with a strong positive correlation r = 0.673 (p-value < 0.05). **Conclusion**: IL-6 level and PSI score have a significant and strong positive correlation, these results suggest that IL-6 can be used as a biomarker to determine the severity of pneumonia patient.

Keywords: Community-Acquired Pneumonia; Interleukin-6; PSI Scores.

Introduction

Pneumonia has a high morbidity and mortality rate worldwide. Community-Acquired Pneumonia (CAP) affects 1.3 million people annually and is the leading cause of severe sepsis and infection-related mortality[1–3] CAP is a disease that requires serious treatment and can be fatal with a high incidence rate, incidents occur from 2 to 12 cases per 1,000 people per year and are a major cause of mortality from infectious diseases.[4] Health is very important to us.[5–8]

In people with CAP, it is very important to assess the severity of early admission because it determines the severity of the disease and subsequent treatment.[3, 9, 10] The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V).[11, 12] These scores represent good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). Pneumonia management is expected to be better, helping clinicians determine the severity of the disease, the need for hospitalization or ICU care, diagnostic evaluation, adequate treatment, and assessment to determine length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

The accuracy of PSI scores and other scores in predicting the outcome of pneumonia sufferers is so doubtful that recently, some biomarkers, pro-inflammatory cytokines, and adrenocortical hormones have been extensively assessed for their effectiveness in assessing the outcomes and severity of the disease. Over the past few years, some markers have been tested as for infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes instead of infections.[11, 13]

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Resti Yudhawati, Evi Yuniawati. Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia. J Adv Pharm Edu Res 2020;10(2):1-6. Source of Support: Nil, Conflict of Interest: None declared.

Interleukin-6 with its pleiotropic function is associated with pathophysiology of various diseases, so researchers assume will be closely related to the measuring the severity of pneumonia (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, congestive heart disease, kidney disease, cerebrovascular disease), physical examination and laboratory examination. The objective of this study was to determine whether there is a correlation between interleukin-6 levels and PSI scores in community-acquired pneumonia patients.

Methods

This research design is an analytic observational with a cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, over 21 years of age, signed informed consent willingly (or indicated by family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Purulent cough is clinically associated with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. Leukocytosis is found on a laboratory examination,and ~~and there is an infiltrating chest or air bronchogram on a chest x-ray~~.

The PSI score is a predictive score for assessing the severity of pneumonia that consist of 20 different variables. The total PSI score was classified into 5 mortality classes (class I - V) based on the patient characteristics profile to determine the risk class.

IL-6 examination was performed using enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. The measurements of interleukin-6 levels in the blood was taken from the patient's venous blood with a 5 cc syringe, then centrifuged for several minutes, the resulting plasma was obtained, then placed in a tube and stored in a refrigerator at -70°C. Measurement of interleukin-6 patient serum was performed by researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Statistical analysis was performed using SPSS software package for windows, version 17.0 (SPSS, Inc., Chicago, IL). Pearson correlation was used to determine the correlation between variables. A p-value of less than 0.05 was considered statistically significant.

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This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

Results

Demographic Data of the Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and a maximum of 86 years. Most patient were in the age group of 51-60 years with 9 patients (34.60%).

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The high PSI score is mostly due to age, sex and the presence of comorbidities, laboratory tests, and radiological examination of the pleural effusion. However, physical examination did not significantly affect the PSI score because some of the physical examination results were still in normal limit (Table 1).

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Male (Age)	18	69.20
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Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35°C or >40°C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80
BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 in patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD score of PSI was 88.58±25.511. The minimum PSI score was 17 and the maximum score was 138 (Table 2).

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels in CAP Patients

In this study, the risk class was PSI score in most patients class III (42.3%) and then followed by class IV (34.6%). Based on the analysis result, the highest level of IL-6 was obtained in PSI class V and the lowest was in class I (Table 3).

Table 3. PSI Score and Mean of IL-6 in CAP Patients

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

According to Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Therefore, Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and a significantly correlated (p-value <0.05) (Table 4).

Table 4. Correlation between Interleukin-6 Level and PSI Score of CAP Patients

	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of the comorbid factors were not calculated in the PSI scores, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) (Table 4).

IL- 6 had a cut-off point of 184,182 with Area Under Curve (AUC) of 28% (95% confidence interval 10.4% -45.6%) with a p-value> 0.05. The cut-off point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The interleukin-6 AUC graph is shown in Figure 1.

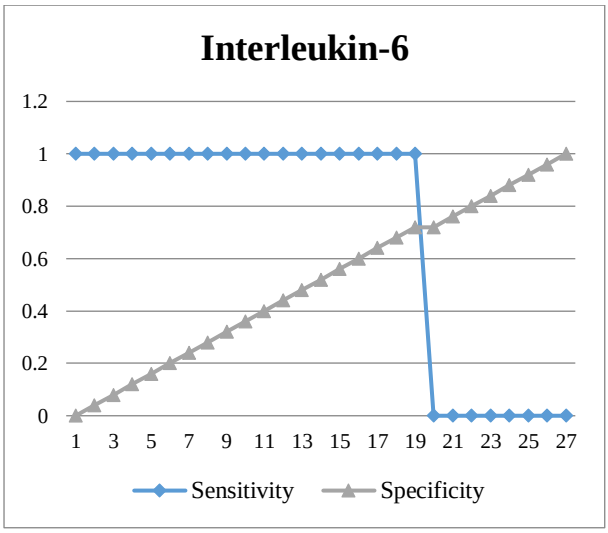

Figure 1. Graph Area Under Curve Interleukin 6

Discussion

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum IL-6 level was 9.92 and the maximum was 106.72. This showed a wide range with a serum level of 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in the cute phase this level of interleukin increases. Recognition of a microorganism through the interaction between Pattern Recognition Receptors (PRRs) and pathogen-associated molecular patterns (PAMPs).[12] These interactions activate various intracellular signal transduction pathways and subsequently activate a variety of transcription factors such as the cytosolic nuclear factor-kappa β (NF-kβ). NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region, and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses.[14, 15]

The results of this study showed that PSI scores have ranges of values from minimum score of 17 and maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which is quite significant. Patients who were hospitalized mainly had PSI class III and IV. This is consistent with the Menendez study of CAP patients with a class III PSI score of 5.6%; class IV was 38.9%; and class V was 55.6%.[16] According to research by Ignatio Martin-Loeches, PSI scores in class IV and V were 63.9%.[17] Many pneumonia patients had scores of III and IV mainly because of the age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the

lowest in class I. Interleukin-6 levels can predict severity, sepsis, and mortality. Similarly, with the relation of IL-6 and comorbid diseases, the more comorbid factors appear, the higher the level of IL-6.

Interleukin-6 levels were positively correlated with PSI scores and was a significant difference. The result of this study were in accordance with the report of Stefano et al., which showed a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05).[18] Otherwise, the result of Menendez study showed that there was no significant association between IL-6 and PSI score with p=0.08 (p-value >0.05).[16]

Interleukin-6 is a multi-functional cytokine that plays a significant role in the body's defense system, as well as its ability to induce the inflammatory response phase.[19] IL-6 is released by T-cells and macrophages due to stimulate the immune response, infection, trauma, burns or tissue damage leading to inflammation. High and persistent level of IL-6 are associated with infection and severity of injury. Interleukin-6 with its pleiotropic function is related to the pathophysiology of various diseases, such as metabolic diseases, cancer, liver disease, heart disease, cerebrovascular disease. Interleukin also affects the aging process.[19]

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores.[20] Therefore, IL-6 levels are closely related to PSI scores in which comorbid diseases and blood sugar levels also affect interleukin-6. According to the above results, it can be concluded that the level of IL-6 in patients with community pneumonia is closely related to the patient's PSI score class. The higher the IL-6 level, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization period.[17] Similarly, according to Menendez et al., IL-6 examination on the first day of hospitalization was closely related to the PSI score class.[16]

In order to know that IL-6 is not affected by comorbid factors or both, correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. This suggests that in addition to its function to reflects tissue or organ damage, IL-6 levels also can be used to determine the severity of pneumonia if the patient's PSI score is doubtful, where comorbid factor unable to be determined yet.

Conclusion

In conclusion, measurement of IL-6 pro-inflammatory cytokines provides information comparable to PSI score. IL-6 Biological markers can help clinicians in identifying the severity of pneumonia and increase the predictive value of mortality to determine early patientmanagement to reduce mortality rate and length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

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Author's contribution

RY and EY designed the study, collected samples, gathered data, analyzed the data, made tables and figures, wrote the manuscript, and contributed to review and revise. All authors have been approved the final version.

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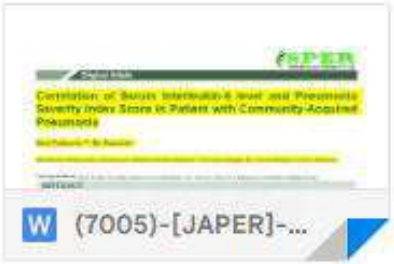

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Original Article

Correlation of Serum Interleukin-6 level and Pneumonia Severity Index Score in Patient with Community-Acquired Pneumonia

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ABSTRACT

Biomarkers of pro-inflammatory cytokines have been widely evaluated for their efficacy in the assessment of disease severity. The pleiotropic functions of Interleukin-6 (IL-6) allow it to induce the inflammatory responses acute phase. This study aimed to evaluate the correlation between PSI scores in patients with CAP and IL-6 levels. The study was a cross-sectional study. 26 pneumonia patients who met the inclusion and exclusion criteria were included in this study. IL-6 levels and PSI scores were calculated on the first day of patients treated.

The mean±SD of PSI scores and IL-6 levels were 161.860±75.0042 and 88.58±25.511 respectively. The cut off point of IL-6 was 184.182 with 28% AUC (95% confidence interval of 10,4% – 45,6%) with p-value > 0.05. There was a significant correlation between the PSI score and interleukin-6 level with a strong positive correlation r = 0.673 (p-value < 0.05). PSI score and IL-6 level have a strong and significant positive correlation, these results suggest that IL-6 can be used as a biomarker to determine the severity of pneumonia inpatient.

Keywords: Community-Acquired Pneumonia, Interleukin-6, PSI Scores, Disease severity

Introduction

Globally, Pneumonia has a high mortality and morbidity rate. Community-Acquired Pneumonia (CAP) affects 1.3 million people annually and is the leading cause of severe sepsis and infection-related mortality [1-3]. CAP is a disease that requires serious treatment and can be fatal with a high incidence rate, incidents occur from 2 to 12 cases per 1,000 people per year and are the main factors of mortality from infectious diseases [4].

In people with CAP, it is very important to assess the severity of early admission because it determines the severity of the disease and subsequent treatment [5, 6]. The consensus of pulmonary infection with the validated scoring risk used is Pneumonia Severity Index (PSI). PSI divided CAP patients into three groups according to mortality risk: low risk (class I-III), medium risk (class IV), and high risk (class V) [3, 7]. These scores represent good predictions and are recommended for use by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA). Pneumonia management is expected to be better, helping clinicians determine the disease severity, the need for hospitalization or ICU care, diagnostic evaluation, adequate treatment, and assessment to determine the length of stay. However, hospitals rarely conduct this examination because it is considered impractical and unable to reflect the inflammatory response directly.

Comprehensive molecular and quantitative bacteriologic testing can greatly improve outcomes, but these techniques are not generally available, and studies using them have been limited to patients who produced valid sputum samples, before prolonged antibiotic therapy [8, 9]. Over the past few years, some markers have been tested for infection and sepsis, but none of the indicators can determine acute bacterial infections or inflammatory processes instead of infections [10].

Interleukin-6 with its pleiotropic function is related with the various diseases' pathophysiology, so researchers assume will be

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How to cite this article: Yudhawati R, Yuniawati E. Correlation of serum Interleukin-6 level and Pneumonia severity index score in a patient with community-acquired Pneumonia. J Adv Pharm Edu Res. 2021;11(2):xx-xx. https://doi.org/

closely related to measuring the severity of pneumonia (PSI score) based on demographic factors, comorbid factors (liver disease, malignant disease, physical examination, kidney disease, cerebrovascular disease), congestive heart disease and laboratory examination. The objective of this study was to evaluate whether there is a correlation between PSI scores and interleukin-6 levels in community-acquired pneumonia patients.

Materials and Methods

This research design is an analytic observational with a cross-sectional study. It was conducted in the pulmonology ward of Dr. Soetomo Hospital Surabaya. Inclusion criteria include patients diagnosed with CAP, over 21 years of age, signed informed consent willingly (or indicated by family) to participate in the study. Exclusion criteria include diagnosed with acute infection of other organs, and patients with pulmonary tuberculosis.

Patients with CAP are acute respiratory infections in the lower respiratory tract that start from outside the hospital. Purulent cough is clinically associated with phlegm, shortness of breath, fever, ronkhi, bronchial or bronchovesicular breath sounds. Leukocytosis is found on a laboratory examination, and there is a pulmonary infiltrate or air bronchogram on a chest x-ray.

The PSI score is a predictive score for assessing the severity of pneumonia that consists of 20 different variables. The total PSI score was classified into 5 mortality classes (class I - V) based on the patient characteristics profile to determine the risk class.

IL-6 examination was performed using the enzyme-linked immunosorbent assay (ELISA) method and had a unit of ng/l. The measurements of interleukin-6 levels in the blood were taken from the patient's venous blood with a 5-cc syringe, then centrifuged for several minutes, the resulting plasma was obtained, then placed in a tube and stored in a refrigerator at -70°C. Measurement of interleukin-6 patient serum was performed by researchers in collaboration with the Laboratory of Infectious Diseases Airlangga University Hospital of Surabaya under applicable Standard Operational Procedure.

Statistics

All data were expressed as mean±SD. Using the SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL), Statistical analysis was performed. The correlation between variables was evaluated Pearson correlation. A p-value of less than 0.05 was considered statistically significant.

Ethical clearance

This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

Results and Discussion

Demographic Data of the Study Subjects

During the study period, 26 patients were eligible. Male patients with CAP were 18 people (69.2%). The mean age was 51.27±14.013 with a minimum age of 27 and a maximum of 86 years. Most patients were in the age group of 51-60 years with 9 patients (34.60%).

Characteristics of PSI Scores for CAP Patients

The high PSI score is mostly due to age, sex, and the presence of comorbidities, laboratory tests, and radiological examination of the pleural effusion. However, the physical examination did not significantly affect the PSI score because some of the physical examination results were still within the normal limit **(Table 1)**.

Table 1. Characteristics of PSI Research Subject

Characteristic	Total	Percentage
Male (Age)	18	69.20
Female (Age - 10)	8	30.80
Orphanage/nursing home (+10)	0	0
Comorbid Disease		
Malignancy disease (+30)	8	30.80
Liver disease (+20)	11	42,30
Congestif Heart Disease (+10)	5	19.20
Cerebrovascular Disease (+10)	1	3.80
Renal Disease (+10)	8	30.80
Physical Examination		
Disturbance of conciousness (+20)	5	19.20
Respiratory rate >30 times/minute (+20)	1	3.80
Sistolic Blood Pressure <90 mmHg (+20)	1	3.80
Temperature <35°C or >40°C (+15)	0	0
Heart rate >125 times/minute (+10)	3	11.50
Laboratory		
pH <7,35 (+30)	1	3.80
BUN >10,7 mmol/L (+20)	0	0
Sodium <130 mEq/L (+20)	2	7.70
Glucose >13,9 mmol/L (+10)	2	7.70
Hematocrit <30% (+10)	5	19.20
O_2 Arterial BP <60 mmHg (+10)	1	3.80
Pleural Effusion (+10)	5	19.20

Interleukin-6 Level and PSI Score of CAP Patients

The mean and standard deviation (SD) level of IL-6 in patients with CAP was 161.860±75.0042. The minimum IL-6 level was 40.71 and the maximum was 364.59. The mean and SD of PSI

score was 88.58±25.511. The minimum PSI score was 17 and the maximum score was 138 **(Table 2)**.

Table 2. Interleukin-6 Level and PSI Scores of CAP Patients

	Mean±SD	Minimum	Maximum
IL-6 Level	161.860±75.0042	40.71	364.59
PSI Score	88.58± 25.511	17	138

PSI Score and Mean of IL-6 Levels in CAP Patients

In this study, the risk class was PSI score in most patients class III (42.3%) and then followed by class IV (34.6%). Based on the analysis result, the highest level of IL-6 was obtained in PSI class V and the lowest was in class I **(Table 3)**.

Table 3. PSI Score and Mean of IL-6 in CAP Patients

PSI Score Class	Total	Mean±SD	Minimum	Maximum
I	2 (7.7%)	59.225±26.18	40.71	77.74
II	2 (7.7%)	72.845±30.12	51.55	94.14
III	11 (42.3%)	161.77±78.52	57.29	364.59
IV	9 (34.6%)	193.612±55.27	145.52	288.33
V	2 (7.7%)	211.11±46.02	178.57	243.65

The Correlation between Interleukin-6 Levels with PSI Scores of CAP Patients

According to the Kolmogorov Smirnov test, IL-6 levels and PSI scores were normally distributed (p-value >0.05). Therefore, the Pearson correlation test was used to determine the correlation between IL-6 levels and PSI scores.

IL-6 levels and PSI Score had a strong positive correlation (0.673) and a significantly correlated (p-value <0.05) **(Table 4)**.

Table 4. Correlation between Interleukin-6 Level and PSI Score of CAP Patients

	Correlation	p-value
PSI Score vs IL-6 Level	0.673	0.000
Interleukin 6 vs PSI Score without comorbid factor	0.546	0.004

In this study, if the characteristics of the comorbid factors were not calculated in the PSI scores, the correlation between IL-6 and PSI scores was strong (0.546) and significantly correlated (p-value <0.05) **(Table 4)**.

IL- 6 had a cut-off point of 184,182 with Area Under Curve (AUC) of 28% (95% confidence interval 10.4% -45.6%) with a p-value> 0.05. The cut-off point that can be used for IL-6 was 184,182. This can be used as a limitation, if the IL-6 level is <184,182, hospitalization of the patients is unnecessary, while if the IL-6 level is >184,182, hospitalization is recommended. The interleukin-6 AUC graph is shown in **Figure 1**.

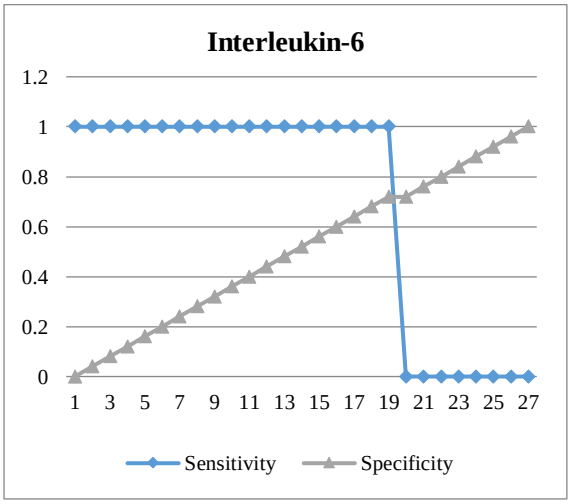

Figure 1. Graph Area Under Curve Interleukin 6

The levels of IL-6 throughout the study subjects were increased. It can be seen that the minimum level of IL-6 was 40.71, while the minimum level of IL-6 ELISA kit was 2 ng/L. This is consistent with the study by Stefano, where the minimum IL-6 level was 9.92 and the maximum was 106.72. This showed a wide range with a serum level of 28.95 pg/ml. Interleukin-6 has a function as an activator of the immune system, in the cute phase this level of interleukin increases. Recognition of a microorganism through the interaction between pathogen-associated molecular patterns (PAMPs) and Pattern Recognition Receptors (PRRs) [11]. These interactions activate various intracellular signal transduction pathways and subsequently activate a variety of transcription factors such as the cytosolic nuclear factor-kappa β (NF-kβ). NF-kβ then moves from the cytoplasm to the cell nucleus and binds to the transcription zone of the promoter region, and triggers the production of various cytokines, for examples TNF-α, IL-1β, IL-6, and IL-10 are classic pro-inflammatory cytokines that also contribute to further responses including activating adaptive immune responses [12, 13].

The results of this study showed that PSI scores have ranges of values from a minimum score of 17 and a maximum of 138. Demographic factors such as age, sex, comorbid factors (malignancy, liver, congestive heart disease, cerebrovascular disease, and kidney disease), cause additional values which are quite significant. Patients who were hospitalized mainly had PSI class III and IV. This is consistent with Martin-Loeches et al. study of CAP patients with a class IV and V had the highest presentation of hospitalized patients, PSI scores in class IV and V were 63.9% [14]. Many pneumonia patients had scores of III and IV mainly because of age and comorbid factors. The highest average of IL-6 was obtained in PSI scores of class V and the

lowest in class I. Interleukin-6 levels can predict severity, sepsis, and mortality. Similarly, with the relation of IL-6 and comorbid diseases, the more comorbid factors appear, the higher the level of IL-6.

Interleukin-6 levels were positively correlated with PSI scores and were a significant difference. The result of this study was in accordance with the report of Stefano *et al.*, which showed a significant association between IL-6 levels and PSI score with p=0,016 (p-value <0.05) [15].

Interleukin-6 is a multi-functional cytokine that plays a significant role in the body's defense system, as well as its ability to induce the inflammatory response phase [16]. Due to stimulating the immune response, trauma, burns, infection, or tissue damage leading to inflammation, IL-6 is released by T-cells and macrophages. High and persistent levels of IL-6 are associated with infection and the severity of the injury. Interleukin-6 with its pleiotropic function is related to the various diseases' pathophysiology [16].

As mentioned earlier, PSI uses 20 variables, including comorbidities (liver disease, heart disease, kidney disease, malignancy, cerebrovascular disease), and age with high scores [3,7]. Therefore, IL-6 levels are closely related to PSI scores in which comorbid diseases and blood sugar levels also affect interleukin-6. According to the above results, it can be concluded that the level of IL-6 in patients with community pneumonia is closely related to the patient's PSI score class. The higher the IL-6 level, the higher the patient's PSI score class. This is in accordance with the research by Ignatio Martin-Loeches et al, it was found that patients who experienced therapy failure had high PSI scores and had long hospitalization periods [14].

To know that IL-6 is not affected by comorbid factors or both, the correlation was tested in this study. IL-6 levels and PSI scores without comorbid characteristics had a strong correlation (0.546) and significantly correlated. This suggests that in addition to its function to reflects tissue or organ damage, IL-6 levels also can be used to evaluate pneumonia severity if the patient's PSI score is doubtful, where comorbid factors unable to be determined yet.

Conclusion

In conclusion, measurement of IL-6 pro-inflammatory cytokines provides information comparable to PSI score. IL-6 Biological markers can help clinicians in identifying the severity of pneumonia and increase the predictive value of mortality to determine early patient management to reduce mortality rate and length of hospitalization. IL-6 marker can be used to improve the prediction of prognosis mortality, based on each patient's inflammatory response.

Acknowledgments: We truly thank the patients who participated in this study and the authorities and staff of Dr. Soetomo Hospital, Surabaya, Indonesia, who helped and supported us during the study.

Conflict of interest: The authors confirm that this article content has no conflict of interest

Financial support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement: This study follows the principles of the Helsinki declaration. Research ethics has been issued by Dr. Soetomo Hospital Surabaya Ethics Committee (Ethical Clearance Number 624/Panke.KKE/XI/2016) before the start of the study.

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I am pleased to inform you that, your peer reviewed revised article entitled: "Correlation of serum Interleukin-6 level and Pneumonia severity index score in patient with community-acquired Pneumonia" is now accepted for publication in (Volume 11, 3) of the Journal of Advanced Pharmacy Education & Research [JAPER].

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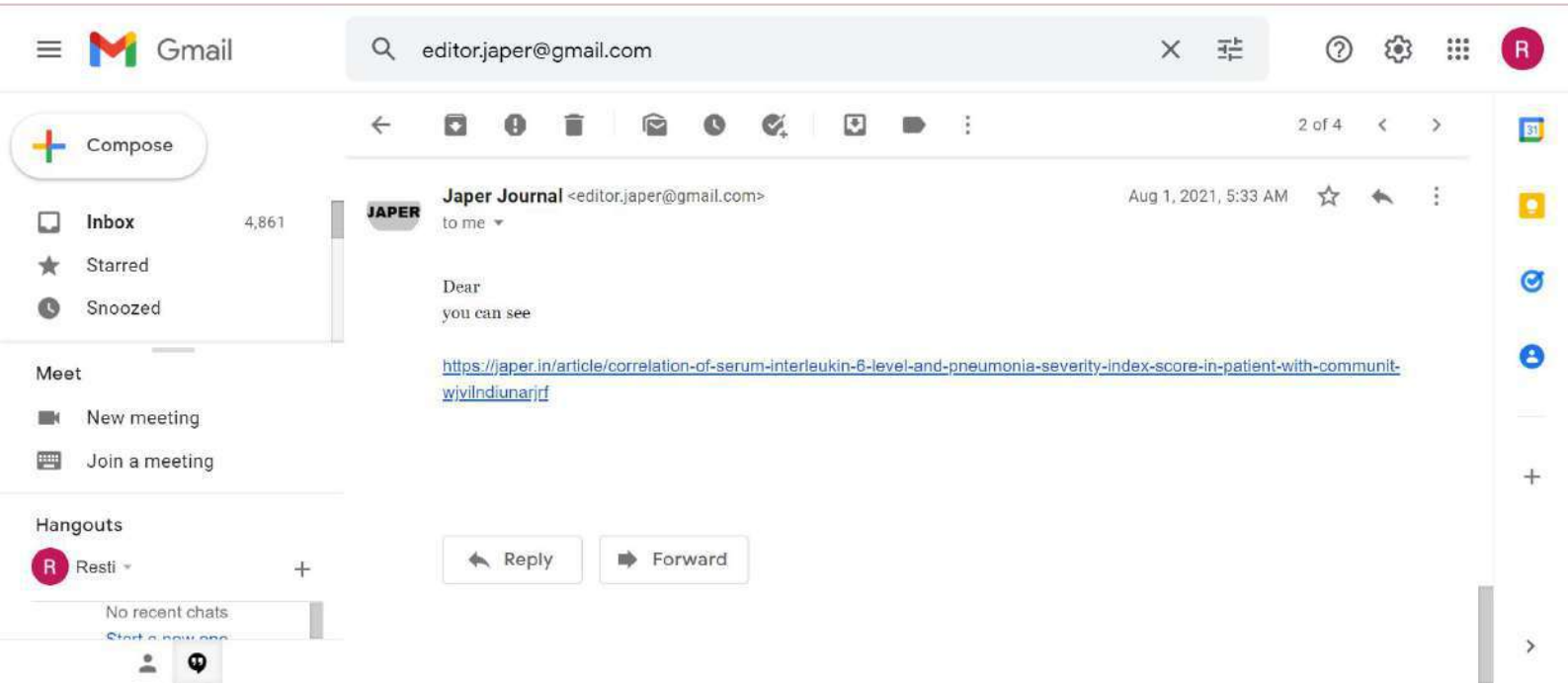
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