PREDICTOR FACTORS FOR 30-DAY MORTALITY IN ADULT HOSPITALIZED CAP WITH IMMUNOSUPPRESSIVE-DOSE GLUCOCORTICOID USE

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ABSTRACT

Background: Glucocorticoids are still frequently used for various conditions such as autoimmune diseases and malignancies, leading to immunosuppression and risk of pneumonia. Pneumonia in the immunocompromised host have a higher mortality rate compared to the immunocompetent population. The clinical manifestations of pneumonia in this population are often atypical, and clinical conditions can deteriorate rapidly compared to the time of admission, making predictors at admission necessary to assess risk mortality.
Objective: To evaluate the PSI score, lymphocyte count, increase in procalcitonin levels, history of chemotherapy, history of other immunosuppressant use, and the presence of comorbid lung disease as predictors of 30-day mortality in hospital-acquired community pneumonia patients using immunosuppressive doses of glucocorticoids.
Method: This study is a retrospective cohort study of subjects diagnosed with community-acquired pneumonia who were treated at RSUPN Dr. Cipto Mangunkusumo with a history of immunosuppressive dose glucocorticoid use. Bivariate analysis was conducted, followed by multivariate analysis of the predictor factors for 30-day mortality.
Results: Among the 267 study subjects, significant predictor factors were found, including a PSI score > 91 (RR 1.873; 95% CI 1.383 – 2.535) with a p-value < 0.001, and increased procalcitonin levels (RR 1.386; 95% CI 1.080 – 1.780) with a p-value of 0.01.
Conclusion: A PSI score > 91 and procalcitonin > 0.76 ng/dl are predictors of 30-day mortality in community-acquired pneumonia patients with a history of immunosuppressive doses of glucocorticoids treated at RSUPN Dr. Cipto Mangunkusumo.

Keywords: immunocompromised host pneumonia, glucocorticoids, 30-day mortality

ABSTRAK
Latar belakang: Glukokortikoid masih sering digunakan sebagai terapi untuk berbagai kondisi seperti penyakit autoimun dan keganasan, di mana penggunannya menyebabkan imunitas menurun dan berisiko infeksi. Pneumonia pada pejamu imunitas menurun (immunocompromised host pneumonia) memiliki angka mortalitas yang tinggi dibandingkan populasi imunokompeten. Manifestasi klinis pneumonia pada populasi ini kadang tidak khas dan kondisi klinis dapat terjadi perburukan yang cepat jika dibandingkan saat admisi, sehingga dibutuhkan prediktor saat admisi untuk menilai mortalitasnya.
Tujuan: Menilai skor PSI, jumlah limfosit, kenaikan kadar prokalsitonin, riwayat kemoterapi, riwayat penggunaan imunosupresan lain, dan adanya penyakit paru penyerta sebagai faktor prediktor mortalitas 30 hari pneumonia komunitas rawat inap yang menggunakan glukokortikoid dosis imunosupresan
Metode: Studi ini merupakan studi kohort retrospektif terhadap subjek dengan diagnosis pneumonia komunitas yang dirawat di RSUPN Dr Cipto Mangunkusumo dengan riwayat penggunaan glukokortikoid dosis imunosupresan. Dilakukan analisis bivariat dan dilanjutkan dengan analisis multivariat terhadap faktor prediktor mortalitas 30 hari.
Hasil: Dari 267 subjek penelitian ditemukan faktor prediktor yang bermakna berupa skor PSI > 91 dengan (RR 1,873; 95% IK 1,383 – 2,535) dengan nilai p < 0,001, dan peningkatan prokalsitonin (RR 1,386; 95% IK 1,080 – 1,780) nilai p 0,01.
Kesimpulan: Skor PSI > 91 dan prokalsitonin > 0,76 ng/dl merupakan faktor prediktor mortalitas 30 hari pneumonia komunitas dengan riwayat glukokortikoid dosis imunosupresan yang dirawat di RSUPN Dr Cipto Mangunkusumo.

Kata kunci: pneumonia pada pejamu imunitas menurun, glukokortikoid, mortalitas 30 hari

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Background

Based on the American Thoracic Society (ATS), immunocompromised-host pneumonia (ICHP) is pneumonia that occurs in individuals with either quantitative or qualitative impairment of the immune system.[1] It accounts for 75% of pulmonary complications in patients with decreased immunity and is one of the leading causes of mortality.[2] Analysis of the Global Initiative for MRSA Pneumonia (GLIMP) database by Di Pasquale found that 18% of patients diagnosed with community-acquired pneumonia had risk factors for decreased immunity.[3] One the most common cause of immunocompromise is the use of glucocorticoids; the prevalence of glucocorticoid use as a cause of immunocompromise in pneumonia patients ranges from 10 – 20% and the mortality rate of pneumonia in immunocompromised patients due to glucocorticoid is up to 22,6%.[3–5] The challenges in treating this population are the relatively non-specific clinical features, rapid deterioration despite relatively stable clinical presentation upon admission, and infection by opportunistic or atypical pathogens.[1] However, glucocorticoid is still widely used for multiple inflammatory and autoimmune related conditions due to its rapid and potent anti-inflammatory effect. The use of glucocorticoids is usually concomitant with other immunosuppressants, chemotherapy, and chronic pulmonary diseases which can further increase the risk of immunosuppression and comorbidities.

Some studies have elaborated the use of scoring systems such as Pneumonia Severity Index (PSI) showing higher severity in the immunocompromised population but limited data observe its use for mortality in this population.[6–8] Other studies showed prognostic factors include lymphocytopenia and the use of other immunosuppressing agents such as DMARDs and chemotherapy with varying results.[7,9,10] Procalcitonin is frequently used to guide diagnosis and therapy but its use as a predictor for mortality is limited. Therefore, our study aim to determine predictor factors for mortality in patients with immunocompromised-host pneumonia due to glucocorticoids.

Methods

A retrospective cohort study was conducted on subjects aged 18 years and older admitted with community acquired pneumonia in Dr. Cipto Mangunkusumo General Hospital. Inclusion criteria were immunocompromise due to glucocorticoids; the criteria for immunosuppressive dose is $\geq$ 20 mg of prednisone or equivalent (PEQ) for 14 days, $\geq$ 10 mg PEQ for 90 days, or $\geq$ 40 mg PEQ for 7 days. Exclusion criteria were patients with HIV, incomplete data from medical records, and refusal of participation. A consecutive sampling was conducted spanning from 2022 – 2024. Independent variables for this study are PSI score $\geq$ 91 (class IV and V) at admission, procalcitonin level at admission, lymphocytopenia (<0,8 x $10^3/\mu l$) at admission, history of chemotherapy up to 3 months prior to admission, use of other immunosuppressants a minimum of 2 weeks prior to admission, and the presence of chronic pulmonary diseases; the dependent variable is 30-day mortality after admission.

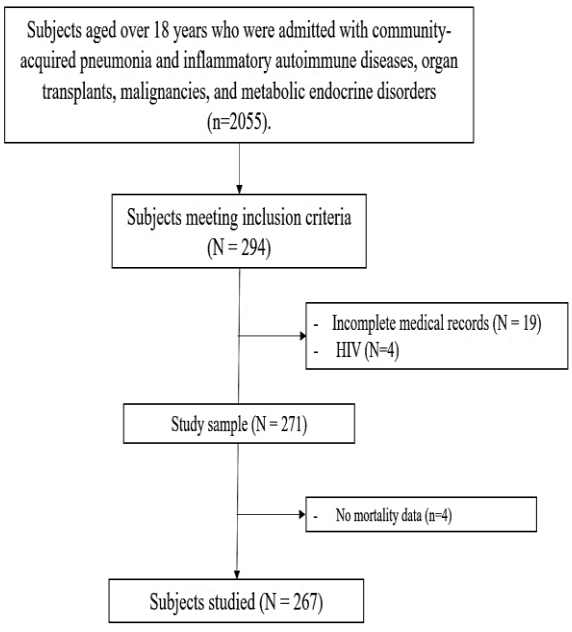

Figure 1. Sampling of subjects

Data analysis was done using STATA; univariate analysis was done to describe subject characteristics, and bivariate analysis using chi-square method was carried to

determine factors with p < 0.25 that will be analyzed using logistic regression. The cut off for procalcitonin level was determined using area under the curve analysis. Ethical approval was issued by the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia (KET-1405/UN2.F1/ETIK/PPM.00.02/2024) and location permit was issued by the Innovation and Intellectual Property Management Installation of the Dr. Cipto Mangunkusumo General Hospital (YR.02.01/D.IX.2.3/1426/2024).

Results

There were 267 subjects involved in this study; there was a higher proportion of females compared to males (56.7%), with a median age of 46 (IQR 29 - 57) years. The most common comorbidities found in the study subjects were autoimmune diseases (136; 50.94%), neoplasms (131; 49.06%), and kidney diseases (112; 41.9%).

Table 1. Subjects characteristics

Variable	Number (n=267)
Age (years), median (IQR)	46 (29 - 57)
Gender, n (%)	
Female	151 (56,77)
Diabetes melitus, n (%)	33 (12,41)
Kidney Diseases, n (%)	112 (41,95)
Chronic Heart Failure n (%)	71 (26,59)
Cerebrovascular diseases, n (%)	71 (26,59)
Liver diseases, n (%)	23 (8,61)
Malignancy, n (%)	131 (49,06)
Hematologic malignancy	64 (23,97)
Non hematologic malignancy	67 (25,09)
Autoimmune Diseases, n (%)	136 (50,94)
Type of autoimmune disease:	
SLE	82 (30,71)
Nephrotic syndrome	11 (4,11)
Myasthenia gravis	7 (2,6)
Autoimmune hemolytic anemia	4 (1,5)
FSGS	4 (1,49)
Immunogenic thrombocytopenic purpura	3 (1,1)
Rheumatoid Arthritis	2 (0,74)
Erythema Nodosum Leprosum	2 (0,74)
Others	18 (6,7)

SLE: systemic lupus erythematosus; FSGS: focal segmental glomerulosclerosis

The median PSI score of the study subjects was 100 (77 - 131), with 162 (60.67%) subjects having a PSI score $\geq$ 91. A total of 67 (25.1%) subjects used immunosuppressants other than glucocorticoids, with the largest number of mycophenolic acid 46 (17.2%) subjects, and for the use of tacrolimus 5 (1.9%) subjects combined with other immunosuppressants. The average duration of use of immunosuppressant drugs was 114 days, with the longest duration of 4 years, and the shortest duration of 14 days. The 30-day mortality for this research subject group reached 51.69%. Based on PSI class, mortality for Class II was 9 (3,37%), Class III 24 (8,9%), Class IV 54 (20,22%) and Class V 51 (19,1%); mortality for Class IV and V was 39,32%.

Table 2. Predictor factors

Variable	Subjects (n=267)
PSI score, median (IQR)	100 (77 – 131)
PSI score ≥91, n (%)	162 (60,67)
Lymphocyte, median (IQR)	0,79 (0,44 – 1,27)
Lymphocytopenia, n (%)	134 (50,19)
PCT, median (IQR)	1,13 (0,24 – 6,17)
History of chemotherapy, n (%)	74 (27,7)
Chemotherapy regimen:	
RCHOP/RCOP	14 (5,2%)
Platinum + Taxan	11 (4,1)
VRD	10 (3,7)
LALA80	6 (2,2)
Cyclophosphamide	4 (1,5)
VCD	3 (1,1)
Others	25 (9,4%)
Chronic pulmonary disease, n (%)	41 (15,36)
Type of chronic pulmonary disease	
Lung malignancy	22 (8,2)
Bullae/Cavity	9 (3,4)
Interstitial lung disease	4 (1,5)
COPD	3 (1,1)
Asthma	3 (1,1)
Bronchiectasis	1 (0,4)
Use of other immunosuppressants, n (%)	67 (25,1)
Type of immunosuppressant n (%)	
Mycophenolic acid	49 (18,4)
Cyclosporine	5 (1,9)
Tacrolimus*	5 (1,9)
Mycophenolate mofetil	4 (1,5)
Azathioprine	3 (1,1)
Methotrexate	1 (0,4)
Mortality	138 (51,69)

RCHOP/RCOP: rituximab, cyclophosphamide, /vincristine, doxorubicin, prednisone; VRD: bortezomib, lenalidomide, dexamethasone; LALA80: chemotherapy regimen for acute lymphoblastic leukemia; VCD: bortezomib, cyclophosphamide, dexamethasone ; COPD: chronic obstructive pulmonary disease. *Tacrolimus was combined with other immunosuppressants

A total of 150 (56.1%) subjects received methylprednisolone, 88 (32.9%) received dexamethasone, 22 (8.2%) subjects received prednisone, and the remainder received a combination of the two types of glucocorticoids. The criteria for immunosuppressive doses equivalent to prednisone > 20 mg/day for 14 days were found in 138 (51.7%) subjects, equivalent to > 30 mg in 7 days in 80 (30%) subjects, and equivalent to > 10 mg for 90 days in 49 (18.4%) subjects.

A total of 136 (50.9%) subjects underwent blood and/or sputum culture tests; 133 (49.81%) subjects underwent blood culture testing, and 107 (40%) subjects underwent sputum culture testing. The most prevalent etiologic pathogen found in sputum culture were *Klebsiella pneumoniae* (20%), *Acinetobacter sp*. (19%), and *Pseudomonas aeruginosa* (14%). Subjects who underwent viral etiology testing were 112 (41.94%), with a diagnosis of COVID-19 established in 19 (7%) subjects, and CMV in 3 (1.12%) subjects. Among those diagnosed with COVID-19, 9 (47%) experienced severe COVID-19. Four (1.4%) subjects underwent galactomannan tests and 3 were diagnosed with aspergillosis, while 1 subject died before the results were available. A total of 37 (13.9%) subjects were diagnosed with pulmonary tuberculosis both before admission and during treatment, with 29 (78.3%) of the subjects diagnosed with pulmonary TB confirmed bacteriologically.

A threshold value for procalcitonin was found to have predictive value > 0.76 ng/dl with AUC 0.645 (0.579 – 0.711) p < 0.0001 sensitivity 68.1% and specificity 55.8%. (Figure 1)

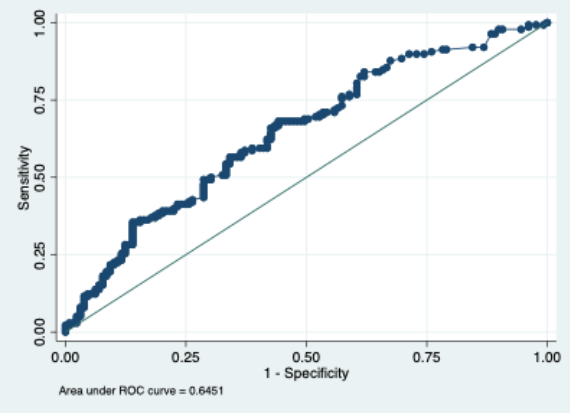

Figure 2. AUC for procalcitonin

In the bivariate analysis of predictor factors for mortality, variables with a P value < 0.25 included PSI score > 91 (RR 2.062; 95% CI 1.521 – 2.796) with p < 0.0001 and elevated procalcitonin 1.390 (95% CI 1.084 – 1.783) with p = 0.009, as well as the use of immunosuppressants RR 0.798 (0.59 – 1.079) with p = 0.144.

After multivariate analysis, significant predictors were found to be PSI score > 91 with RR 1.873 (95% CI 1.383 – 2.535) p < 0.001 and elevated procalcitonin RR 1.386 (1.080 – 1.780) p = 0.01.

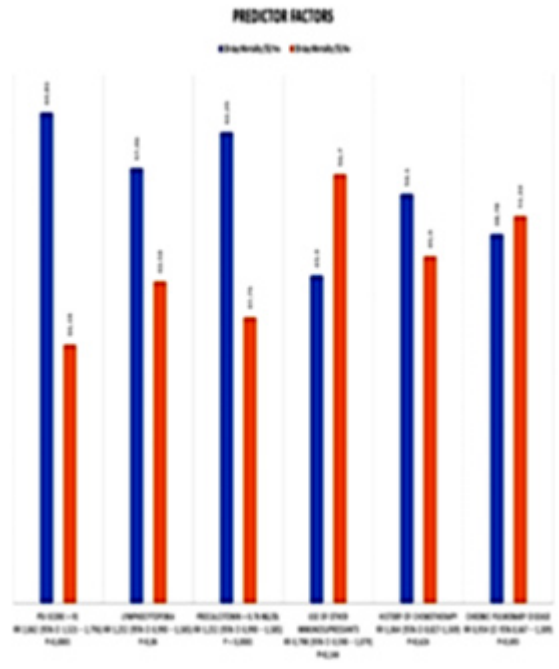

Figure 1. Predictor Factor Analysis. Analysis was done using Chi-Square Test

Table 3. Logistic regression of predictor factors

Variable	RR (95% IK)	P value
First step		
PSI score ≥91	1,829 (1,347 – 2,484)	<0,0001
Lymphocytopenia	1,113 (0,901 – 1,376)	0,318
Increased procalcitonin	1,377 (1,072 – 1,769)	0,012
Use of other immunosuppressants	0,858 (0,649 – 1,133)	0,282
Second step		
PSI score ≥91	1,836 (1,352 – 2,492)	<0,0001
Increased procalcitonin	1,408 (1,097 – 1,806)	0,007
Use of other immunosuppressants	0,865 (0,655 – 1,148)	0,310
Final step		
PSI score ≥91	1,873 (1,838 – 2,535)	<0,0001
Increased procalcitonin	1,386 (1,080 – 1,780)	0,010

Discussion

In this study, the subjects were predominantly female, and concomitant immunocompromising conditions were autoimmune diseases (50,94%) and malignancy (49,06%). Based on the severity, 60,67% subjects have PSI score of ≥ 91 (classes IV and V). The median procalcitonin value was 1,13 ng/dl and lymphocyte 0,79 x 10^3/µl. Subjects with history of chemotherapy were 27,7%, prior use of other immunosuppressants were 25,1%, and coexisting chronic pulmonary disease was 15,36%. This study found mortality rate in adult hospitalized patients with immunocompromised-host pneumonia due to glucocorticoids were 51,69%. Predictor factors that were found to be statistically significant were PSI score of ≥ 91 and increased procalcitonin ≥ 0.76 ng/dl.

In this study, the mortality rate of the subjects is significantly higher than prior studies in immunocompromised host pneumonia, which

ranged between 22,6 – 24%.[6–8] This study was conducted in a tertiary hospital in Jakarta, where complex cases were referred from multiple peripheral centers. Moreover, testing for viral and fungal etiologies were not covered by the National Health Insurance, which might lead to underdiagnosis. Microbiological data showed etiologies were not typical for community acquired infections, which might also lead to undertreatment upon admission, which shows antibiotics used did not cover these pathogens.

PSI score of ≥ 91 was shown to be a predictor for 30-day mortality in this population, with mortality of 39,32% which is higher than in the general population of 10,7%.[11] This result is in accordance with studies in other immunocompromised patients from multitude of causes and in cancer patients.[12,13] Study by Gonzalez et al showed PSI have sensitivity of 82% and specificity of 34% for 28 day mortality.[13]

Procalcitonin, which is usually used for diagnosis and guiding therapy, was also found to be a predictor factor with a cut-off value of > 0.76 ng/dl; higher than the cut off value from previous studies of > 0.25 ng/dl for ICU patients in a study by Kim et al.[14] However, study by Sedef et al showed procalcitonin of > 2 ng/dl is a predictor for mortality in cancer patients, with AUC 0,753, sensitivity 66%, specificity 76%.[15] This finding might be caused by different characteristics of subjects, where in the study the subjects are more heterogenous compared to study by Sedef et al, but could have more comorbidities which leads to more severe infection compared to subjects in the study by Kim et al.[14,15]

Lymphocytopenia was not found to be a predictor for mortality in this population. Lymphocytopenia in community acquired pneumonia is an acknowledged phenotype which suggest immune dysregulation and increased risk of mortality in immunocompetent patients; the cut-off of which is < 0.724 x 10^3/µL.[16] Studies in immunocompromised host pneumonia also showed lymphopenia (0,8 – 1 x 10^3/µl) as a predictor for mortality.[9,17] However, a study by Yang et al found lymphopenia is not a predictor factor for mortality in immunocompromised patients with severe pneumonia in the ICU.[18] In this study, all subjects were immunocompromised due to glucocorticoid use, which affects lymphocyte and their subsets through lympholysis, decreased activity, proliferation, and maturation, and reduced production of cytokines and antibodies. Therefore, the number of lymphocytes alone cannot represent the lymphocyte dysfunction caused by glucocorticoids.

The use of chemotherapy was not a predictor for mortality in this population. Prior studies shown mortality after induction chemotherapy ranges between 17 – 45%.[19,20] The mechanism of which chemotherapy cause mortality in pneumonia includes neutropenia, lymphocyte dysfunction, and barrier dysfunction through mucositis.[21] Population study by Zheng et al showed highest pneumonia mortality among cancer patients after chemotherapy was found in patients with ALL, AML, dan intracranial malignancy.[20] However, a study by Varnai et al found no difference in mortality of patients admitted for Covid-19 with a history of chemotherapy up to 4 weeks before admission.[22] Our findings might be caused by the heterogeneity of the subjects, where only 12% of subjects have AML or ALL, and the subjects have heterogenous chemotherapy regimens. As Varnai et al stated in their study, performance status, which was not evaluated in this study, might affect the mortality outcome; cancer patients with poor performance status might have their chemotherapy delayed compared to their more robust counterparts.

Chronic pulmonary disease was not found to be a predictor for mortality in this study. Present studies regarding this matter showed varying results; COPD was not found to be a predictor for mortality of inpatient community acquired pneumonia despite higher risk of intensive care treatment, longer length of stay, and use of mechanical ventilation.[23,24] However, underdiagnosis in COPD is estimated to be significant due to limited resources.[25,26] Other studies showed ILD and lung cancer are associated with higher

mortality due to bacterial pneumonia and COVID-19. 27,28 In this study, our findings might reflect the heterogeneous nature of the chronic pulmonary disease found in our subjects and the underdiagnosis of chronic pulmonary diseases such as COPD.

The use of other immunosuppressants other than glucocorticoids was not found to be a predictor in this study. Similar findings were reported by Li et al; a study by Vaidie et al comparing mortality in the ICU also found no difference in mortality between subjects with long term immunosuppressants.[7,29] Furthermore, studies on subjects with immunosuppressants such as transplant receiver (Kalil et al) and autoimmune diseases (Sedef et al) admitted for bacterial infections with or without admission of intensive care unit showed lower mortality compared to control subjects.[30,31] Dysregulated inflammatory cytokine associated with sepsis associated with worse outcome, whereas the use of immunosuppressants might suppress certain deleterious cytokines. However, studies by both Kalil and Sedef et al were conducted on a more homogenous subjects, whereas the subjects in this study and in the study by Vaidie et al were more heterogenous, which might cause the insignificance of the findings.

This study is a novel study elucidating predictor factor for mortality in this population in Indonesia. PSI is a relatively feasible scoring system to apply in clinical pathways for this population as an attempt to stratify risks for intensive care and possibility of more aggressive treatments. However, procalcitonin is not as available in other centers and therefore is limited to tertiary hospitals in Indonesia. Limitations of this study include inability to determine whether subsets of lymphocyte such as CD4+ and other cytokine dysregulation is a predictor factor for mortality. The study subject is heterogenous, which might cause the insignificance of some of the potential predictor factors in this study. Due to the retrospective nature of the study, multiple factors such as appropriate antibiotics and proper timing of their administrations, availability of intensive care unit and/or mechanical ventilation, and decision of do-not-resuscitate (DNR) cannot be assessed. This study also has all-cause mortality outcome and therefore cannot exclude nosocomial causes and other causes that can contribute as the cause of mortality; limited resource regarding viral and fungal diagnostic examination leading to underdiagnosis can also contribute to the outcome. Future studies should put these limitations in consideration in the design to yield better results.

Conclusion

PSI and an increased procalcitonin of $\geq$ 0,76 ng/dl are predictors for 30-day mortality in subjects admitted for community-acquired pneumonia with a history of immunosuppressant dose glucocorticoid use.

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Conflict of Interest

Authors declare no conflict of interest

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