Validation of Drug Resistance in Pneumonia (DRIP) Score as Empirical Antibiotic Failure Predictor in Community-Acquired Pneumonia Patients in Cipto Mangunkusumo Hospital

Rohayat B Simanjuntak[1]*, Khie Chen Lie[2], Cleopas M Rumende[1], Murdani Abdullah[3], Hamzah Shatri[4], Soekamto Koesnoe[5], Leonard Nainggolan[2], Aulia Rizka[6]

[1]Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Tropical Medicine and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Division of Psychosomatic, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[5]Division of Allergy and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[6]Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Rohayat B Simanjuntak MD. Division of Tropical Medicine and Infectious Disease, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: dr.rohayat@gmail.com.

ABSTRACT

Background: *The incidence of CAP due to Drug-Resistant Pathogen (DRP) requires broad-spectrum antibiotic therapy, Drugs Resistance in Pneumonia (DRIP) score can predict these cases. The use of the DRIP score can prevent antibiotic failure and long hospitalization, but validation is needed so that the DRIP score can be used according to the local community at Cipto Mangunkusumo National Central Public Hospital.* ***Methods:*** *This research is a retrospective cohort study in CAP patients who were hospitalized during the period January 2019 to June 2020. Data were taken from medical records. Failure of empiric antibiotics occurs when one of these criteria is found: patient mortality, ICU transfer, and escalation of antibiotics as well as length of stay.* ***Results:*** *480 patients met the criteria. There were 331 patients (69%) with a DRIP score of <4 and 149 patients (31%) with a DRIP score of≥4. A total of 283 patients (59%) of antibiotic failures were detailed in 174 patients with a DRIP score <4 and 109 patients DRIP score ≥4. DRIP calibration using the Hosmer-Lemeshow test obtained p-value= 0.667 (p>0.05). AUC observations on the ROC curve obtained 0.651 (95% CI; 0.601-0.700).* ***Conclusion:*** *The DRIP score has low accuracy performance and calibration value in predicting empirical antibiotic failure and poor discriminatory value.*

Keywords: *DRIP score, antibiotics failure, Drug-Resistant Pathogens, Community-Acquired Pneumonia.*

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the major causes of mortality and morbidity in the world impacting substantial health and economic[1]. CAP is still commonly found in Indonesia with an incident rate of 1.8% while in Jakarta with an incidence of 2.4% which exceeds the national rate.[2] The bacterial pathogens causing CAP vary according to the characteristics and geographic location of the host, rapid identification and recognition of CAP, can improve outcomes and reduce the risk of death.[3]

The use of appropriate antibiotics becomes a very important preventive and curative effort for successfully resolving MDR (Multidrug Resistance) and interventions against the complexity of resistance, at least slowing the rate of MDR occurrence.[4] In recent years, several cases of CAP have been associated with the emergence of Drug-Resistant Pathogens (DRP). DRP requires different antibiotic therapy compared to the empiric antibiotics recommended in the CAP therapy guidelines. Against DRP pathogens, the initial empirical antibiotics given include antipseudomonal and anti-MRSA. A large number of risk factors associated with DRP have been identified by research worldwide, currently classified into four categories: (1) Pathogen acquisition, (2) Persistent colonization, (3) selective pressure on resistant organisms, and (4) Invasion lower respiratory tract.[5]

The Drug Resistance in Pneumonia (DRIP) score was published in the United States in 2016 by Webb as a predictive model with the most external validation compared to other prediction methods. The study shows that the DRIP score has better predictive accuracy compared to several other alternative scoring systems. The DRIP score is composed of ten risk factors associated with DRP pathogens, including history of antibiotic use, length of hospital stays, enteral nutrition, history of DRP pathogen infection with previous, history of previous medication, chronic lung disease, poor functional status, gastric acid suppression, wound care, and history of MRSA colonization.[5] In recent study in Jakarta showed that the DRIP score had good predictions for assessing drug-resistant pathogens in CAP, patient characteristics, and patterns of bacteria in RSUPN Dr. Cipto Mangunkusumo Jakarta.[6]

There is a need for new and better methods to predict drug-resistant antibiotics while restricting unnecessary widespread use of antibiotics.[7] The decreased use of broad-spectrum empiric antimicrobials will increase by 9% if using the DRIP score.[8] In the pneumonia population with an increase in the prevalence of CAP-DRP, inadequate initial antibiotic therapy is associated with poor outcomes, including death. Overtreatment with antibiotics is preferable for inadequate empiric therapy given the poor outcome evidence. Additional studies are needed to guide the safe and timely de-escalation of antibiotics in patients with antibiotic cultures at moderate to high risk of CAP-DRP.

We hypothesized that the accuracy of the DRIP score as a predictor of failure of empiric therapy and length of stay of CAP patients treated at RSUPN Dr. Cipto Mangunkusumo.

METHODS

The study was a retrospective cohort design that was performed at Cipto Mangunkusumo National Central Hospital, Jakarta, Indonesia by the review ethics review committee University of Indonesia Medical Faculty (Number: KET-1250/UN2.F1/ETIK/PPM.00.02/2022), data collection was done from November to December 2022 by tracing the medical records of community-acquired pneumonia patients who were hospitalized from January 2019 to June 2020. The consecutive sampling method was used and the inclusion criteria included: 1) CAP patients who were hospitalized; 2) Age ≥18 years; 3) Administer empirical antibiotics when the patient is admitted to the hospital. Data were excluded if there was a history of administration of meropenem antibiotics and incomplete data. DRIP score variable data or risk factors were collected from medical records with a score <4 included in the low-risk group and a score ≥4 included in the high-risk group. The definition of empiric antibiotic failure is determined when one of the following variables is found: 1) antibiotic escalation; 2) transfer to the ICU; or 3) patient' mortality. Quantitative data were analyzed with SPSS version 22.

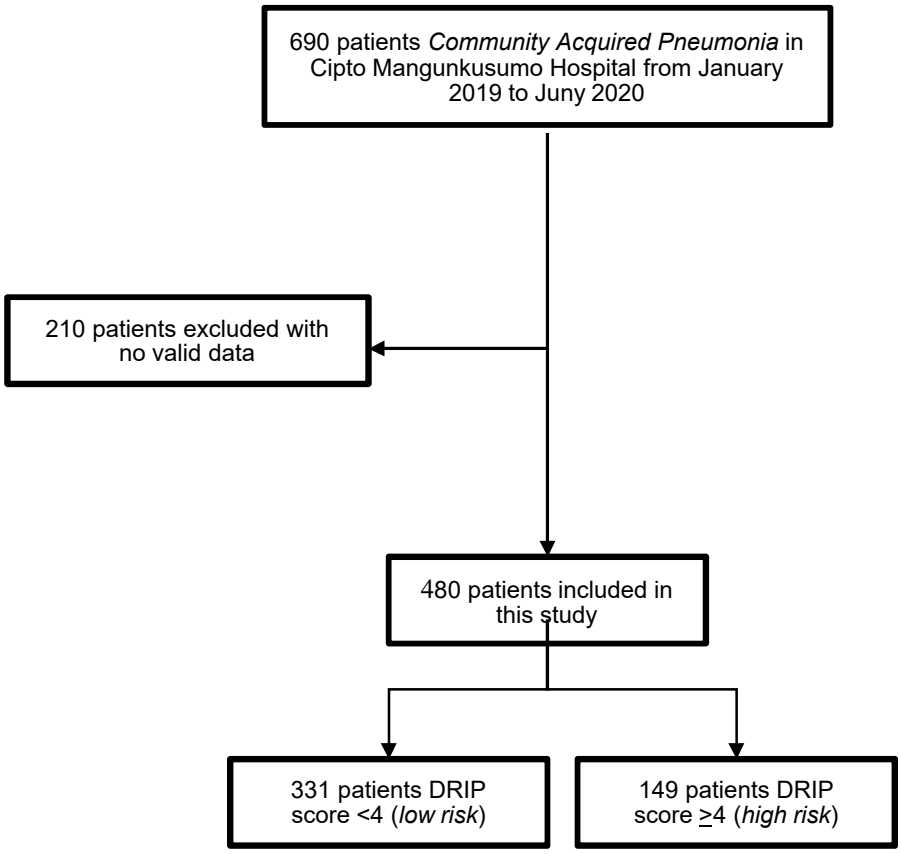

Figure 1.

RESULTS

There are 480 patients included as research subjects. Overall, most patients were in the 18–60-year age group, as well as in the DRIP score group <4; but in the DRIP score group ≥4 more in the age group> 60 years. There were more males than females, both in the DRIP score <4 (low risk) and DRIP score ≥4 (high risk).

Diabetes mellitus is the most common comorbid (27.1%) found in both groups. Poor functional status was found in all study subjects (100%), this happened because all hospitalized patients were considered to have poor functional status according to this study's operational definition. There was no data found for MRSA colonization in all study subjects. The most common risk factor was a history of gastric acid suppression (36.5%), followed by enteral nutrition (25.1%) and a history of hospitalization (17.1%). Risk factors for previous history of infection with drug-resistant pathogens (DRP), were only found in 11 patients (2.3%) who had previous treatment data at RSCM and had culture examination results.

In **Table 2** of the empiric antibiotic failure factor, it was found that of the 141 people who experienced mortality, 90 people (63.8%) had a DRIP score <4, while the remaining 51 people (36.2%) had a DRIP score ≥4. From **Table 2** can be seen that the length of stay of all community pneumonia patients in both groups had a median value of 9 days, quartile 1 was at 6 days and quartile 3 was at 16 days. The high-risk group had a median value of 9 days with quartile 1 at 5 days and quartile 2 at 16 days.

Table 3 shows that the failure of empiric antibiotics in community-acquired pneumonia patients is more than the success of empiric antibiotics, as many as 283 patients (59.0%) experienced empiric antibiotic failure. In the DRIP score <4 group, the proportion of failure (52.5%) was higher than the success of empiric antibiotics (47.5%). In the DRIP score group ≥ 4 it was found that there were more failures (73.2%) than successes of empiric antibiotics therapy (26.8%).

Table 1. Characteristics of high and low-risk patients with community-acquired pneumonia.

Characteristic	n=480 (%)	DRIP Score	
		<4 n= 331 (%)	≥4 n= 149 (%)
Demographic cireteria			
Age(years), median (IQR)	59 (47.89-59)	58 (46-68)	61 (51.5-70.78)
Age, n (%)			
18-60 year	257 (53.5)	185 (55.9)	72 (48.3)
>60 year	223 (46.5)	146 (44.1)	77 (51.7)
Gender, n (%)			
Men	256 (53.3)	175 (52.9)	81 (54.4)
Women	224 (46.7)	156 (47.1)	68 (45.6)
Comorbidities, n(%)			
Diabetes Melitus	130 (27.1)	89 (26.9)	41 (27.5)
Malignancy, n (%)	120 (25)	76 (23)	44 (29.5)
Chronic Kidney Disease, n (%)	108 (22.5)	71 (21.5)	37 (24.8)
Cerebrovascular Disease, n (%)	84 (17.5)	46 (13.9)	38 (25.5)
Congestive Heart Failure, n (%)	75 (15.6)	54 (16.3)	21 (14.1)
Chronic Liver Disease, n (%)	34 (7.1)	19 (5.7)	15 (10.1)
Chronic Lung Disease, n (%)	27 (5.6)	13 (3.9)	14 (9.4)
DRP Risk Factor in DRIP Score			
Antibiotic use within 60 days			
0	416 (86.8)	322 (97.6)	94 (63.1)
2	63 (13.2)	8 (2.4)	55 (36.9)
Long-term care resident			
0	407 (84.8)	324 (97.9)	83 (55.7)
2	73 (15.2)	7 (2.1)	66 (44.3)
Tube feeding			
0	359 (74.9)	276 (83.6)	83 (55.7)
2	120 (25.1)	54 (16.4)	66 (44.3)
Drug-resistant pathogens pneumonia within a year			
0	467 (97.7)	328 (99.4)	139 (93.9)
1	2 (0.4)	1 (0.3)	1 (0.7)
2	9 (1.9)	1 (0.3)	8 (5.4)
Hospitalization within 60 days			
0	398 (82.9)	312 (94.3)	86 (57.7)
1	82 (17.1)	19 (5.7)	63 (42.3)
Chronic pulmonary disease			
0	455 (94.5)	320 (96.7)	135 (90.6)
1	25 (5.2)	11 (3.3)	14 (9.4)
Poor function status			
0	0 (0)	0 (0)	0 (0)
1	480 (100)	331 (100)	149 (100)
Gastric Acid Suppression Use			
0	305 (63.5)	244 (73.7)	61 (40.9)
1	175 (36.5)	87 (26.3)	88 (59.1)
Active wound care			
0	440 (91.7)	314 (94.9)	126 (84.6)
1	40 (8.3)	17 (5.1)	23 (15.4)
MRSA colonization within one year			
0	480 (100)	331 (100)	149 (100)
1	0 (0)	0 (0)	(0)

Table 2. Empiric antibiotic failure factors.

Outcome	Total	DRIP Score	
		<4	≥4
Antibiotik escalation, n (%)			
No	262 (54.6)	201 (60.7)	61 (40.9)
Yes	218 (45.4)	130 (39.3)	88 (59.1)
Transferred to ICU, n (%)			
No	449 (93.5)	306 (92.4)	143 (96)
Yes	31 (6.5)	25 (7.6)	6 (4)
Mortality, n (%)			
No	339 (70.6)	241 (72.8)	98 (65.8)
Yes	141 (29.4)	90 (27.2)	51 (34.2)
Length of stay (days), Median (IQR)	9 (6-16)	10 (6-16)	9 (5-16)

Table 3. Empiric antibiotics failure on DRIP score.

Outcomes	Total	DRIP Score	
		<4	≥4
Empiric Antibiotic Therapy			
Success	197 (41.0)	157 (47.4)	40 (26.8)
Failure	283 (59.0)	(2.6)	109 (73.2)

The DRIP score performance is determined from the calibration and discrimination values. In this study, the calibration of the Drug Resistance in Pneumonia Score (DRIP) as a predictor of empirical antibiotic therapy failure can be assessed by comparing the two expected and observed groups. In the Hosmer-Lemeshow test, p=0.667 where the DRIP score has a good calibration based on the statistical significance of the Hosmer-Lemeshow test (p>0.05).

Discrimination ability The DRIP score has an AUC (area under the curve) value on the ROC curve obtained: AUC 0.651 (95% CI; 0.601-0.700). The AUC value of 0.6-0.7 indicates that the DRIP score has a poor discriminatory value in predicting failure of empiric antibiotic therapy (transfer to ICU, antibiotic escalation, and mortality) in CAP patients. At a cut-off value of ≥ 4, the DRIP score can differentiate between high and low-risk groups with a sensitivity value of 38.52%, a specificity of 79.70%, a positive predictive value of 73.15, a negative predictive value of 47.43, a positive likelihood ratio of 1.9, and negative likelihood ratio 0.77.

Table 4. DRIP Score Calibration in Expected and Observed Groups (n=480).

		Empiric Antibiotic Failure	
Score	N	Observed	Expected
1	2	1	0.738
2	147	61	66.229
3	90	53	48.153
4	92	59	56.817
5	82	55	56.895
6	67	54	54.168

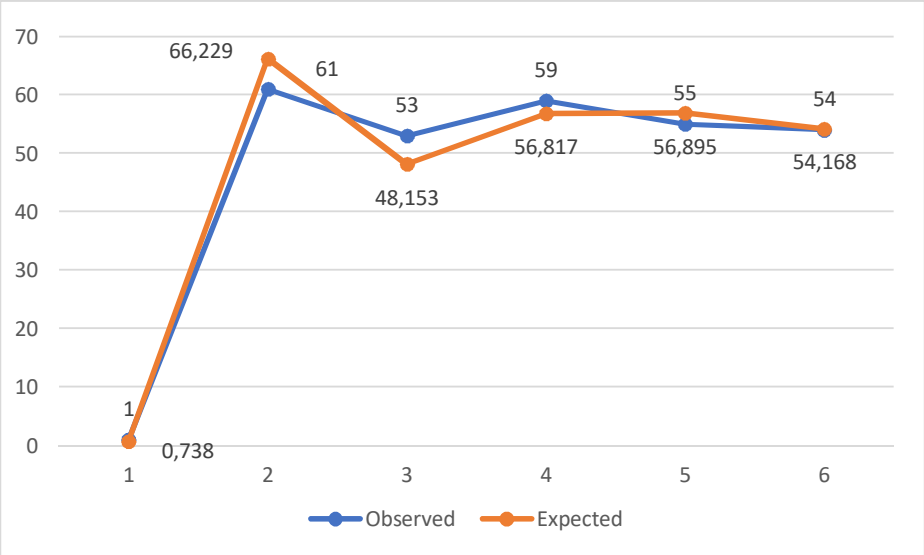

Figure 1. Graphic of DRIP Score Calibration in the Expected and Observed Groups.

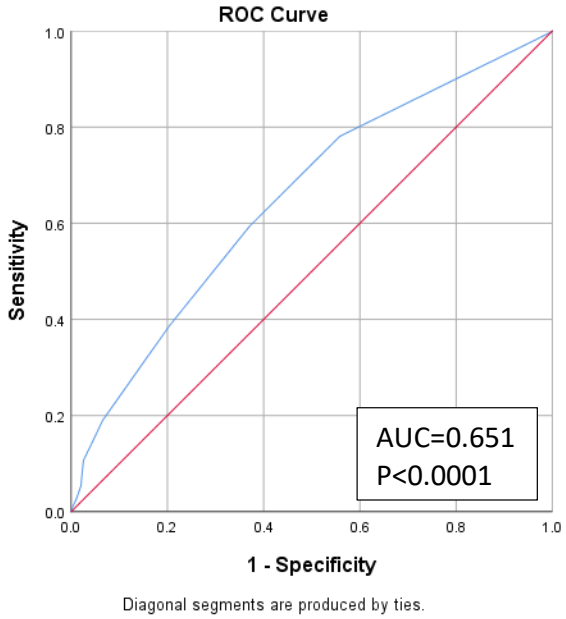

Figure 2. ROC Curve of DRIP Score Validation.

In **Table 5** the distribution of the data of length of stay CAP patients treated at Cipto Mangunkusumo Hospital Jakarta were skewed. The relationship test with data that was not normally distributed was carried out using the Mann-Whitney test. Length of stay of CAP patients treated in Cipto Mangunkusumo General Hospital was not related to DRIP (p=0.483).

Table 5. Mann Whitney Test DRIP Score with Length of Treatment.

Variable	Skor DRIP		p Value
	Low Risk	High Risk	
Length of Stay, Median (IQR)	9 (6-16)	9 (5-16)	0.438

DISCUSSION

In this study, although not much different, the incidence rate of CAP was higher in males compared to females. This can happen due to men's smoking habit in the region. In the age category, the number of respondents aged 18-60 years was 53.5%, not too far off and almost comparable to those aged over 60 years which reached 46.5%. Older age is a risk factor for CAP in the community, where they will have more risks which make them susceptible to CAP and have a much worse prognostic tendency compared to a younger age.[9]

Most of the empirical antibiotics used were dominated by non-pseudomonal antibiotics. Previous study stated that the actual use of ceftriaxone alone has the same effective effect compared to the combination of azithromycin in treating CAP. The appropriate choice of initial antibiotic for community-acquired pneumonia patients in the low-risk class (DRIP score <4) is a combination of Ceftriaxone and Azithromycin, while for high-risk (DRIP score ≥4) the use of β-lactam anti pseudomonas antibiotic combined with vancomycin and azithromycin are more recommended.[10]

Antibiotic escalation in the DRIP score <4 groups was performed on 48.1% of respondents, while in the DRIP score ≥4 groups it was performed on 59.1% of respondents. The study stated that the possibility of determining the escalation of antibiotics was carried out by considering the clinical conditions and comorbid factors present in the patient when the treatment was carried out.

In this study the low-risk group has more transfers to the ICU than the high-risk group, it is possible that this data was caused by an unequal number between the DRIP score group <4 and the DRIP score group ≥4. We assume that because the DRIP score indicator does not show the transfer of community pneumonia patients to the ICU, the DRIP score is not quite accurate in seeing and predicting the occurrence of the transfer of patients to the ICU.

This study found that 141 people died with 90 (63.8%) of them having a DRIP score <4, while 51 (36.2%) had a DRIP score ≥4. The findings of this study indicate that the low-risk group has more mortality than the high-risk group. This is compatible with Babbel's study (2018) which showed that only 3 patients (7%) in the hospital mortality category had a high risk of infection due to drug-resistant pathogens in community pneumonia. We assume that this is due to the severity of CAP and the patient's comorbidities at the time of admission to the ER.

Length of stay of all CAP patients in both groups with a mean of 12 days and a median of 9 days, with an interquartile of 6 days to 16 days. The high-risk group had a median of 9 days with an interquartile of 5 days to 16 days. This is compatible with a previous study with a mean length of stay of 11.5 days and a median of 9 days with an interval of 7 days to 14 days.[11]

As far as the authors know, this is the first study in Indonesia to examine the validation of the DRIP score associated with empirical antibiotic failure and the length of stay of CAP patients. This validation test is very important to do before it is used in the clinical practice of health services, considering that there will be differences in patient characteristics. This research is a retrospective study by taking medical record data, so there is an information bias factor. Some of the limitations of this study are incomplete data related to the DRIP score variable in medical records such as previous MRSA colonization.

Assessment of internal validity is carried out by paying attention to whether the sample obtained (actual study subjects) can represent the desired sample according to the selection criteria (intended sample). The validity of this selection was assessed from the sampling method and predetermined selection criteria, both inclusion and exclusion. The sampling method in this study as a whole was carried out consecutively, which is the best sampling method for the category of non-probability sampling. In this study, 480 subjects were successfully recruited. On this basis, the internal validity of this study was considered quite good.

CONCLUSION

A study has been conducted to determine the accuracy of the DRIP score in CAP patients at Cipto Mangunkusumo National Central Hospital.

The DRIP score has low accuracy performance and calibration value in predicting empirical antibiotic failure and poor discriminatory value.

CONFLICT OF INTEREST

No potential conflict of interest in this study

ACKNOWLEDGMENTS

This research is an operational and innovation grant research at Cipto Mangunkusumo National Central Hospital (RSCM) in 2022.

REFERENCES

1. Rider AC, Frazee BW. Community Acquired Pneumonia. Emerg Med Clin Am. 2018;36:665-83.
2. Rumende CM, Chen LK, Karuniawan A. Hubungan antara ketepatan pemberian antibiotik berdasarkan alur gyssens dengan perbaikan klinis pasien pada pneumonia komunitas. J Penyakit Dalam Indones. 2019;6(2):71.
3. Rothberg MB. Community-acquired pneumonia. Ann Intern Med. 2022;175(4):ITC49-ITC64.
4. Lardo S, Chen LK, Santoso WD, Rumende CM. Hubungan kualitas penggunaan antibiotik menggunakan alur gyssens dengan keberhasilan pengobatan pada sepsis MDR gram negatif di rumah sakit tersier. J Penyakit Dalam Indones. 2021;7(4):221.
5. Cao B, Huang Y, She DY. Diagnosis and treatment of community-acquired pneumonia in adults: 2016 clinical practice guidelines by the Chinese Thoracic Society, Chinese Medical Association. Clin Respir J. 2018;12(4):1320-60.
6. Fadrian F, Chen K, Kumalawati J, Rumende CM, Shatri H, Nelwan EJ. The validation of drug resistance in pneumonia (DRIP) score in predicting infections due to drug-resistant pathogens in community-acquired pneumonia at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Acta Med Indones. 2021;53(4):416-22.
7. Webb BJ, Dascomb K, Stenehjem E, Dean N. Predicting risk of drug-resistant organisms in pneumonia: Moving beyond the HCAP model. Respir Med. 2015;109(1):1-10.
8. Oliver MB, Fong K, Certain L, Spivak ES, Timbrook TT. Validation of a community-acquired pneumonia score to improve empiric antibiotic selection at an academic medical center. Antimicrob Agents Chemother. 2021;65(2):1-7.
9. Almirall J, Serra-Prat M, Bolíbar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. Respiration. 2017;94(3):299-311.
10. Webb BJ, Sorensen J, Mecham I. Antibiotic use and outcomes after implementation of the drug resistance in pneumonia score in ED patients with community-onset pneumonia. Chest. 2019;156(5):843-51.
11. Garau J, Baquero F, Pérez-Trallero E. Factors impacting on length of stay and mortality of community-acquired pneumonia. Clin Microbiol Infect. 2008;14(4):322-9.