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

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ABSTRACT

Background: *The emergence of drug-resistant pathogens (DRP) in recent years possibly contributes to the common problems associated with community-acquired pneumonia. However, to predict the risk of the ailment, the DRIP score is mainly applied, although no validation study has been reported in Indonesia. Therefore, the score prediction accuracy in the population, patient characteristics and germ patterns appears indefinite, particularly for Cipto Mangunkusumo Hospital, Jakarta. The purpose of this study is to determine the DRIP performance as an instrument in predicting infections due to drug-resistant pathogens (DRP) in community-acquired pneumonia at Cipto Mangunkusumo Hospital.* ***Methods:*** *This research employed a cross-sectional design, where the subjects were community-acquired pneumonia patients treated between January 2019 and June 2020. In addition, adequate medical records of the participants were obtained. The condition is defined as DRP when the sputum culture results show resistance to non-pseudomonal β-lactam antibiotics, macrolides, and respiratory fluoroquinolones. Furthermore, the score performance was analyzed by determining the calibration and discrimination values, using the Hosmer-Lemeshow test and AUROC, respectively.* ***Results:*** *A total of 254 subjects were known to have satisfied the selection criteria. These participants were categorized into DRP and non-DRP groups, with 103 (40.6%) and 151 (59.4%) patients, correspondingly. The DRIP calibration analysis using the Hosmer-Lemeshow test obtained p-value = 0.001 (p <0.05), while an AUC value of 0.759 (CI 95%,*

0.702-0.810) was derived from the ROC curve. However, at a score of ≥ 4, the DRIP showed sensitivity, specificity, positive and negative predictive values of 70.9, 92.7, 86.9, and 82.3%, respectively. ***Conclusion:*** *The DRIP score demonstrated a significant performance in predicting infections due to DRP in community-acquired pneumonia.*

Keywords**:** *DRIP score, resistant pathogens, community-acquired pneumonia.*

INTRODUCTION

In recent years, frequent community-acquired pneumonia problems have been linked to the emergence of drug-resistant causative pathogens.[1,2] Drug-resistant pathogens (DRP) require different antibiotics compared to the initial empiric antibiotics recommended in the guidelines for community-acquired pneumonia. Subsequently, for DRP pathogens, the initial empiric antibiotics administered include antipseudomonal and anti-MRSA.[1,3] However, there are a total of 14 alternative score models in addition to the HCAP criteria that are used for the prediction of infection by DRP pathogens in community-acquired pneumonia that has been published, from 2004 till date.

The DRIP (Drug resistance in Pneumonia) score published in the United States by Webb in 2016 is a predictive model with the most external validation tests and implementation research compared to other prediction models.[4] According to research conducted by Webb in 2016, the DRIP score has better predictive accuracy of DRP pathogens compared to several other alternative scores, such as Schreiber, Schorr, Niedermann, Shindo, Aliberti, Park, PES, and HCAP scores, with an AUC value of 0, 88 (95% CI 0.82-0.93).[5] The DRIP score consists of ten risk factors associated with DRP pathogens, including the history of antibiotic use, long-term hospital stay, enteral nutrition, history of infection with previous PRO pathogens, history of previous treatment, chronic lung disease, poor functional status, gastric acid suppression, wound care, and history of MRSA colonization.[5]

Several institutions have performed validation tests and implemented the DRIP score as a new predictive model to replace the HCAP criteria. Based on various research on the implementation of the DRIP score in patients suffering from community-acquired pneumonia, it was concluded that the use of the DRIP score was more effective than the HCAP criteria in helping clinicians avoid the unnecessary use of broad-spectrum antibiotics.[6,7,8] However, this research also recommends that each institution validate it prior to regular use, as the predictive value of this DRIP score will be relatively different depending on the population, region, patient characteristics, and bacterial pattern.

To date, there has been no research in Indonesia that validates or uses a predictive model to predict infection by DRP pathogens in community-acquired pneumonia. Therefore, this research aims to determine the performance of the DRIP score as an instrument to predict infection due to DRP pathogens in patients suffering from community-acquired pneumonia. Furthermore, by knowing the performance of the DRIP score, it is hoped that it will help clinicians in selecting the initial empiric antibiotics in community-acquired pneumonia if they are to use broad-spectrum antibiotics that include antipseudomonal or not in such a way that the patient outcome will be better.

METHODS

The cross-sectional method was used in this research at the Dr. Cipto Mangunkusumo National Central General Hospital from April to May 2021. Furthermore, secondary data in the form of medical records of the patients with community-acquired pneumonia that were hospitalized from January 2019 to June 2020 were used. The population is community-acquired pneumonia patients that are hospitalized at Dr. Cipto Mangunkusumo Hospital. The study has been approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia (Reference No. 226/UN2.F!/ETIK/PPM.00.02/2021).

A sequential sampling method was used and the inclusion criteria include: 1) patients hospitalized with community-acquired pneumonia; 2) age ≥18 years; 3) initial empiric

antibiotics were administered at the time of admission, and 4) sputum specimens were collected for culture and antibiotic sensitivity testing within 2x24 hours after admission. An example of an exclusion criterion was that the inadequate quality of the sputum culture samples, and incomplete data.

Data on DRIP score variables or risk factors are collected from medical records, with a score greater than 4, corresponding to a high risk group with DRP, while a score less than 4 corresponds to a low risk group with DRP. The definition of a drug-resistant pathogen (DRP) is given when the results of sputum cultures and antibiotic susceptibility tests show that a pathogen is resistant to non-pseudomonal beta-lactam antibiotics (Ceftriaxone, Cefotaxime, Ampicillin Sulbactam) and respiratory fluoroquinolones (Levofloxacin, Moxifloxacin).

Statistical Analysis

The data analysis was performed using SPSS 22.0. The basic and clinical characteristics of the research subjects are presented in tabular form. The validation test or the performance of the DRIP score for predicting infection due to DRP pathogens in community-acquired pneumonia was assessed by determining the calibration value with the Hosmer-Lemeshow test and the discrimination value with the area under the curve (AUC) of the ROC curve. The calibration is adequate if the p-value of the Hosmer-Lemeshow test is greater than 0.05. Furthermore, the discrimination value is good if the AUC value is greater than or equal to the minimum expected AUC value (greater than 80%).

RESULTS

In this research, out of 694 patients with community-acquired pneumonia that had sputum culture results from medical records, 440 were excluded because the culture specimens were invalid, and 254 were included as subjects. However, the infection due to DRP pathogens in community-acquired pneumonia was less than non-DRP. There were 103 patients (40.6%) with DRP pathogenic infections, while 151 patients (59.4%) were classified as non-DRP. The demographic and clinical characteristics of the subjects, as well as the proportion of research subjects in both DRP and non-DRP groups based on risk class DRIP scores, can be seen in full in **Table 1**.

Table 2. shows that a total of 323 isolates were obtained, indicating that 131 (40.6%) were classified as DRP and 192 (59.4%) were classified as non-DRP.

The performance of the DRIP score was determined from the calibration and discrimination values. As shown in **Table 3** and **Figure 1**. The value of $p=0.001$ ($p<0.05$) was obtained from the Hosmer-Lemeshow test. This shows that the calibration value of the DRIP score was not good. Meanwhile, the discriminatory ability of the DRIP score toward DRP pathogens was quite good with an AUC value of 0.759 (95% CI; 0.702-0.810) on the ROC curve, as shown in **Figure 2**.

DISCUSSION

The prevalence of patients with community-acquired pneumonia caused by DRP pathogens was 40.6%. The prevalence of DRP Pathogens in community-acquired pneumonia was found to vary in various regions and areas, namely 7.2-36.0% in the Asia Pacific region, 20.0-45.2% in America, and 5.9-33.0% in Europe.[9] For Southeast Asia, the data in the Philippines is 29.7%.[6]

In this research, it was found that the incidence of DRP pathogen infection increased along with the higher risk class according to the DRIP score. Based on these data, it is shown that the DRIP score can predict infection with DRP pathogens in community-acquired pneumonia. This is in line with 2016 Webb research that compared DRIP scores with HCAP criteria. Furthermore, it was stated that the DRIP score ≥ 4 can effectively distinguish low and high risks in community pneumonia due to infection with DRP pathogens, with a sensitivity of 0.82, specificity of 0.81, and a positive predictive value (PPV) of 0.68, and a negative predictive value (NPV) of 0.90, compared to the HCAP criteria, which had a lower predictive value with a sensitivity of 0.79, specificity of 0.65, PPV 0.53 and NPV 0.86.[5]

In this research, the calibration of the DRIP score based on the Hosmer-Lemeshow test has

Table 1. Demographic and clinical characteristics of community-acquired pneumonia patients due to DRP and non-DRP pathogens.

Variables	All Subjects n=254 (%)	DRP Pathogens n=103 (%)	Non DRP Pathogens n=151 (%)
Gender, n (%)			
- Male	143 (56,3)	63 (61,2)	80 (53,0)
- Female	111 (43,7)	40 (38,8)	71 (47,0)
Age, n (%)			
- 18-60 years old	165 (65,0)	60 (58,3)	105 (69,5)
- >60 years old	89 (35,0)	43 (41,7)	46 (30,5)
Comorbidities, n (%)			
- Malignancy	70 (27,5)	28 (27,2)	42 (27,8)
- Diabetes Mellitus	57 (22,4)	25 (24,3)	32 (21,1)
- Cerebrovascular disease	43 (16,9)	23 (22,3)	20 (13,2)
- Chronic Kidney Disease	42 (16,5)	16 (15,5)	26 (17,2)
- Chronic Heart Disease	30 (11,8)	9 (8,7)	21 (13,9)
- Chronic Lung Disease	12 (4,7)	6 (5,8)	6 (3,9)
- Chronic Liver disease	12 (4,7)	6 (5,8)	6 (3,9)
- Other Comorbidities	14 (5,5)	3 (2,9)	11 (7,3)
- No Comorbiditities	7 (2,7)	2 (1,9)	5 (3,3)
Severity			
- No Sepsis	169 (66,5)	70 (68,6)	99 (65,1)
- Sepsis	30 (11,8)	9 (8,8)	21 (13,8)
- Sepsis Shock	55 (21,7)	23 (22,6)	32 (21,1)
Use of Ventilators, n (%)			
- Using a ventilator	49 (19,3)	23 (22,3)	26 (17,2)
- No ventilators	205 (80,7)	80 (77,7)	125 (82,8)
Initial Empirical Antibiotics, n (%)			
- Ceftriaxone-Azitromisin	75 (30,2)	22 (22.5)	53 (35.6)
- Cefotaxime-Levofloxacin	46 (18,6)	24 (24.5)	22 (14.8)
- Ceftriaxone	45 (18,1)	14 (14.3)	31 (20.8)
- Cefepime	21 (8,5)	7 (7.1)	14 (9.4)
- Meropenem	12 (4,9)	8 (8.2)	4 (2.7)
- Ampicillin Sulbactam	11 (4,4)	6 (6.1)	5 (3.4)
- Levofloxacin	9 (3,6)	5 (5.1)	4 (2.7)
- Meropenem-Levofloxacin	9 (3,6)	5 (5.1)	4 (2.7)
- Cefepime-Levofloxacin	9 (3,6)	5 (5.1)	4 (2.7)
- Cefoperazone	3 (1,2)	0 (0.0)	3 (2.0)
- Cefotaxime-Azitromisin	3 (1,2)	0 (0.0)	3 (2.0)
- Ceftazidime	3 (1,2)	2 (2.0)	1 (0.6)
- Cefotaxime	1 (0.4)	0 (0.0)	1 (0.6)
- Moxifloxacin	0 (0,0)	0 (0.0)	0 (0.0)
Antibiotic escalation, n (%)			
- Yes	83 (32.7)	50 (48.1)	33 (21.8)
- No	171 (67.3)	53 (51.9)	118 (78.2)
DRIP Score, n (%)			
- DRIP Score of ≥ 4 (High Risk of DRP)	84 (33.1)	73 (70.9)	11 (7.3)
- DRIP Score of < 4 (Low Risk of DRP)	170 (66.9)	30 (29.1)	140 (92.7)

a p-value of 0.001. The p-value <0.05 indicates that the DRIP score shows a weak correlation between the expected infection by the pathogenic DRP or the expected DRP with the observed results (**Figure 3**). In the Hosmer-Lemeshow test, there was a statistically significant difference ($p<0.05$) between the predicted results of infection due to pathogenic DRP of the DRIP scores and the actual observations obtained from this research. Furthermore, it was also found that the incidence of DRP pathogen infection in community-acquired pneumonia did not increase along with the increase in the total DRIP score. Meanwhile, in the DRIP score discrimination

Table 2. Gram-positive and negative bacteria as the cause of community-acquired pneumonia.

	All Isolates n=323 (%)	DRP Isolate n=131 (%)	Non-DRP isolate n=192 (%)
Gram Positive	52 (16.1)	21 (16.1)	31 (16.1)
- S. epidermidis	17 (5.3)	9 (6.9)	8 (4.2)
- S. aureus	15 (4.6)	2 (1.5)	13 (6.8)
- S. saprophyticus	10 (3.1)	5 (3.8)	5 (2.6)
- E. faecalis	9 (2.8)	5 (3.8)	4 (2.1)
- S. sciuri	1 (0.3)	0 (0.0)	1 (0.5)
Gram Negative	271 (83.9)	110 (83.9)	161 (83.9)
- K. pneumonia	99 (30.7)	41 (31.3)	58 (30.2)
- P. aeuruginosa	53 (16.4)	14 (10.7)	39 (20.3)
- Acinetobacter sp.	51 (15.8)	23 (17.6)	28 (14.6)
- E. coli	27 (8.4)	16 (12.2)	11 (5.7)
- A. baumannii	13 (4.0)	5 (3.8)	8 (4.2)
- E. cloacae	11 (3.4)	4 (3.1)	7 (3.6)
- Enterobacter sp.	9 (2.8)	2 (1.5)	7 (3.6)
- K. oxytoca	6 (1.9)	4 (3.0)	2 (1.1)
- A. xylosoxidants	1 (0.3)	1 (0.8)	0 (0.0)
- S. maltophilia	1 (0.3)	0 (0.0)	1 (0.5)

Table 3. Calibration of DRIP score in the expected and observed groups (n=254).

		DRP Pathogen (%)	
Score	**n**	**Observed**	**Expected**
1	111	30.00	19.620
2	17	0.00	5.255
3	42	0.00	20.263
4	67	59.00	44.230
5	17	14.00	13.632

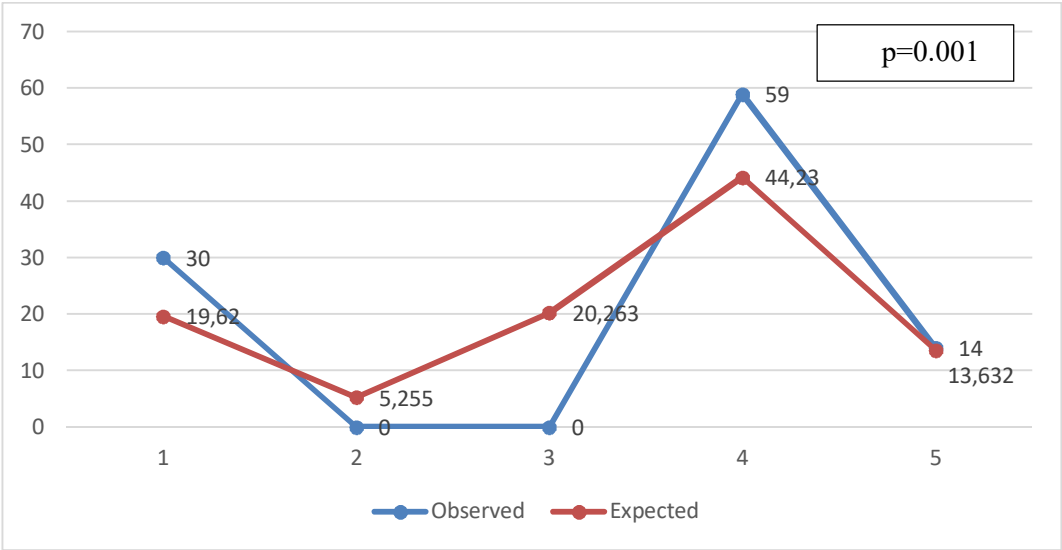

Figure 1. Graph of DRIP score calibration in the expected and observed groups.

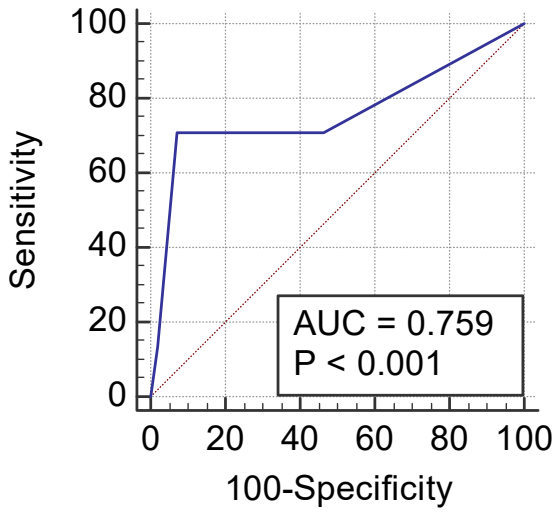

Figure 2. ROC curve of DRIP score model validation.

test, discrimination performance was obtained with an AUC value of 0.759 (95% CI; 0.702-0.810) on the ROC curve. The AUC value of 0.7-0.8 indicates that the DRIP score has a good value in predicting infection due to DRP pathogens in community pneumonia. With a cut-off value of ≥ 4, the DRIP score can differentiate high-risk groups with a low risk of being infected with DRP pathogens with a sensitivity value of 70.9%, specificity of 92.7%, the positive predictive value of 86.9%, the negative predictive value of 82.3%, the positive likelihood ratio of 9.73 and negative likelihood ratio of 0.31.

The calibration value was found to be poor, while the discrimination value with an AUC of 0.759 was good enough to predict infection by DRP pathogen in community-acquired pneumonia. The value of sensitivity, specificity, positive predictive value, and negative predictive value was also obtained quite well. This research aims to determine the ability of the DRIP score to predict infections of community-acquired pneumonia was caused by a DRP pathogen or not. In other words, this study acts as a diagnostic predictive research of DRIP scores in predicting DRP in community-acquired pneumonia. Therefore, the discriminated value of the ROC curve is more suitable to be guided than the calibration value, before the score is applied in daily clinical practice.[10]

Based on the value of AUC, sensitivity, specificity, positive prediction, and negative prediction obtained, it can be concluded that the DRIP score has a good value in predicting community-acquired pneumonia due to a DRP pathogen. This is not different from several other research that validates and implement the DRIP score. Furthermore, Farkas et al stated that the DRIP score was used as a tool in predicting the incidence of infection due to DRP pathogens in community-acquired pneumonia. In this research, the coefficient value was 5.62 (95% CI; 1.07-21.54), and the Hosmer Lemeshow test obtained p<0.0001. The coefficient value indicates that the trend of intervention with broad-spectrum antibiotics in the DRIP score ≥ 4 group was 5.62 times higher than the DRIP score <4 group. It was concluded that the application of the DRIP score for patients suffering from community-acquired pneumonia succeeded in reducing the use of broad-spectrum antibiotics.[11] In another cohort research conducted by Webb et al that implemented the DRIP score in 2,169 patients, the AUC value was 0.79 (95% CI; 0.65-0.93) on the ROC curve. This value indicates that the DRIP score has a good value in predicting infection due to DRP pathogens in community-acquired pneumonia.[12]

In retrospective research carried out by Babbel et al, it was stated that the DRIP score is a new predictive tool developed to identify patients suffering from community-acquired pneumonia with an increased risk of DRP pathogens. Furthermore, DRIP scores have better performance characteristics than other available predictive tools that have been associated with the increased use of broad-spectrum antibiotics.[13] This was also stated in prospective research

Supplementary Table. DRIP score.

Risk Factors	Score
Major	
Antibiotic use within previous 60 days	2
Residence in a long-term-care facility	2
Tube feeding	2
Prior infection with a DRP (1 year)	2
Minor	
Hospitalization within previous 60 days	1
Chronic pulmonary disease	1
Poor functional status	1
Gastric acid suppression	1
Wound care	1
MRSA Colonization (1 year)	1
Total score	14

carried out by Villalobos et al, that showed the performance of the DRIP score in predicting pneumonia due to DRP pathogens. Furthermore, the DRIP score is a good predictive model, which can be used to reduce the irrational use of broad-spectrum antibiotics among low-risk patients.[6]

With the good performance of this DRIP score, this score can be used in patients suffering from community-acquired pneumonia as an instrument for predicting infection due to DRP pathogens, therefore the initial empiric antibiotic selection can be more appropriate.

CONCLUSION

The DRIP score has good performance in predicting infection due to drug-resistant pathogens in community-acquired pneumonia in the population, patient characteristics, and germ or bacterial patterns at the National Central General Hospital of dr. Cipto Mangunkusumo Jakarta.

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