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RESPIRATORY Science

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Original Article

Programmed Death Ligand 1 (PD-L1) Expression in Lung Adenocarcinoma Patients

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Abstract

Background: Programmed Death Ligand 1 (PD-L1) is a protein found in tumor cells that could inactivate T-cells. This research was done to identify the characteristics of lung adenocarcinoma patients to PD-L1 expression in Medan.

Method: Descriptive research with a cross-sectional design was used and the study was done for 12 months (January – December 2018). Sample's collection was done at RSUP (Central Public Hospital) H. Adam Malik and the samples diagnosed with lung adenocarcinoma based on histopathological subtyping were sent to the laboratory of Dharmais Jakarta Hospital where the Ventana 22C3 Immunohistochemistry Staining was done.

Results: Staining was done in 52 samples at Dharmais Jakarta Hospital and only 35 samples were deemed acceptable. In this study, participants' ages ranged from 40 to 60 years, where the majority were male patients, 31 (88.6%) and 33 patients (82.5%) were at an advanced stage (III and IV).

Conclusion: The study found that the PD-L1 expression was mostly observed in male at the age range of 40 – 60 years and stage IV lung adenocarcinoma patients with Tumour Proportion Score (TPS) of 1 – 49%.

Keywords: Programmed Death Ligand 1 (PD-L1), lung adenocarcinoma, Tumour Proportion Score (TPS), Immunohistochemistry

INTRODUCTION

Lung cancer is considered the leading cause of death worldwide, and the Global Cancer Observatory (Globocan) predicted there were approximately 234,555 deaths in Indonesia due to this disease.[1] Lung adenocarcinoma is one of the more commonly found type of lung cancer.[2] According to Melindawati (2008), lung cancer patients in H. Adam Malik Central Public Hospital have increased by 378 within 2004–2008. Based on the cell types, non-small cell lung cancer (NSCLC) is the most common type (99%), which is further

classified into adenocarcinoma (56.3%), squamous-cell carcinoma (40.7%), and large-cell carcinoma (2%), whereas the remaining 1% is identified as small cell lung cancer (SCLC).[3]

The growth of this disease has led to the breakthrough in immunology research to increase the life expectancy in lung cancer patients with lung adenocarcinoma type. The interaction between the immune system and tumor cells during disease progression could induce metastasis.[4,5]

A study by Igarashi (2018) showed that the alveolar macrophages in the tissue specimens from tumor cells were stained with Programmed Death Ligand 1 (PD-L1) and administration of inhibitor in PD-L1 and PD-1 was suggested to increase the life expectancy in advanced stage lung cancer patients. PD-L1 expression is used as a biomarker to predict the patients' positive response to immunotherapy. The understanding of PD-L1 as a biomarker can be reviewed by using different protein with different PD-L1 antibody, a scoring system known as Tumour Proportion Score (TPS), which calculate the percentage of viable tumor cells showing partial or complete membrane staining (>1+) relative to the available tumor cells within the sample (positive and negative), and the interaction between Programmed Cell Death Protein 1 (PD-1) and PD-L1 therapy with immunotherapy clinical trial.[6]

METHOD

A cross-sectional design was used in this study with sample characteristics of patients that have been diagnosed with lung adenocarcinoma based on histopathological subtyping at H. Adam Malik Central Public Hospital within January–December 2018. The collected specimens that have met the inclusion criteria, such as lung adenocarcinoma diagnosis based on histopathological subtyping, were sent to the Laboratory of Anatomical Pathology at Dharmais Jakarta Hospital and rechecked by the assigned pathologists. Immunohistochemistry staining was done afterward, and the specimens were classified into four different types based on the TPS score, which were >50% (strong positive expression), 1–49%, <1% and 0%. This study has been approved by the Ethical Research Committee of the Faculty of Medicine, Universitas Sumatera Utara.

RESULT

Based on inclusion criteria, only 35 out of the 52 samples were accepted and studied further, 17 samples could not be identified due to insufficient tumor cells. The data showed that the subject characteristics were in the age range of 40–60 years, the majority being male, 31 patients (88.6%). Sixteen patients (45.7%) were identified as light smokers based on the low Brinkman Index (BI) and 33 patients (82.5%) were in an advanced clinical stage (III and IV). The details could be seen in Table 1.

It can be seen from table 2 that more than half of the patients (51.4%) obtained a TPS of 1–49%, followed by TPS of >50%

in 8 patients (22.9%), 0% in 6 patients (17.1%) and <1% in 3 patients (8.6%).

Table 1. Characteristics distribution based on gender, age, smoking status, and clinical cancer stage.

Characteristics	Frequency n=35	Percentage (%)
Gender		
Male	31	88.6
Female	4	11.4
Age		
40-60	20	57.1
60	15	42.9
Clinical Stage		
IIIA	2	5.7
IIIB	5	14.3
IIIC	2	5.7
IVA	24	68.6
IVB	2	5.7

Table 2. TPS Distribution of PD-L1

TPS	Frequency n=35	Percentage (%)
0%	6	17.1
<1%	3	8.6
1-49%	18	51.4
≥50%	8	22.9

DISCUSSION

The results showed the majority of lung adenocarcinoma patients in this study were male, 31 (88.6%) and only 4 patients were female (11.4%). A similar trend was seen in the study by Azuma et al. which reported 91 out of the 164 participants were male (55%). Lung cancer was the second most malignant type of cancer observed in men (13.4%) after nasopharyngeal cancer (13.63%) and was the main leading cause of death in men (28.94%). Research by Janzic et al. showed that more than half (63%) of the patients, which was 34, were male and only 20 patients (37%) were female.[4,5]

The age distribution of the participants was mostly within 40 – 60 years. A study suggested that the incidence of lung cancer remained low at the age <40 years although it would increase with age up until 70 years.[7] Median age of the patients in research by Azuma et al. was 66 years (39–82 years)[5] whereas Lin et al. reported a median of 56 years (34–78 years) at the time of diagnosis.[7]

The numbers of patients with clinical stage of IIIA, IIIB, IIIC, IVA, and IVB were reported to be 2 (5.7%), 5 (14.3%), 2 (5.7%), and 24 (68.6%), and 2 (5.7%), respectively. Sixty-seven patients (40.8%), 46 (28%), and 51 (31%) were at stage I, II, and III, respectively in a study by Azuma et al.[5] Lin et al. reported the patients at stage I, II and III were 50 patients (29.4%), 43 (25.3%), and 77 patients (45.3%), respectively. The study suggested that higher tumor stage showed a higher significance in PD-L1 expression and it was confirmed to be an independent factor on the higher incidence of the expression significantly. Furthermore, Lin et al. reported that the highest PD-L1 expression was observed in patients at the advanced stage (III and IV), which were 21 subjects (63.4%).[7]

The TPS score on PD-L1 expression showed that most patients, 18 (51.4%), obtained a score of 1 – 49%. A study by Zhang et al. suggested that higher incidence of PD-L1 expression were observed in male, smokers, and advanced-stage lung cancer patients.[8]

There are several limitations to our study, data were collected based on

observational and retrospective, lack information about the previous treatment to patients, the most of the samples were found minimally or insufficient to be stained.

We would like to thank IASTO and the Laboratory of Anatomical Pathology of Dharmais Hospital for their help and support in this research.

CONCLUSION

The study has reported that the age range of the lung adenocarcinoma patients was 40–60 years, with the majority being male, 31 patients (88.6%). Furthermore, 16 patients were identified as light smokers based on the low BI (45.7%) and 33 participants were in an advanced clinical stage (III and IV) (82.5%).

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Original Article

Implementation Of Clinical Pathway For Management of COPD Exacerbation

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Abstract

Background: The effectiveness for reducing the length of stay and produce better outcomes has been applied with the use of the clinical pathway. In this study, we observe the implementation of clinical pathways (CP) and evaluate their effectiveness in the management of Chronic Obstructive Pulmonary Diseases (COPD) exacerbation in Goenawan Partowidigdo Pulmonary Hospital (RSPG) Cisarua Bogor.

Method: This research is a quantitative study with an analytical survey method and cross-sectional design. Data collection was carried out by studying documentation on 304 medical record files from early 2019 to July 2020 and clinical pathway forms.

Results: There were differences in clinical outcomes before and after the implementation of CP. The difference in the overall mean length of stay (LOS) using CP were 4 days while the who did not use CP were 6 days. For In-Hospital Mortality (IHM) there was 1 death in the CP group, and there were no deaths in non-CP groups. As for the Readmission Rate (RR), the results of the study showed that the most RR was in the CP group, which were 6 patients (54.5%) in 1st wards, 5 patients (62.5 %) in 2nd wards and 39 patients (70.9%) in 3rd wards. These RR results showed that CP of COPD exacerbation must be evaluated further. The average total hospital rate showed a significant difference between the two clinical methods. The hospital rate variable had a very significant difference between the CP and non-CP methods, with a significant value of = 0.0001.

Conclusion: The application of CP can reduce the length of stay (LOS) and the average total hospital rate of patients who are hospitalized for COPD exacerbation. This CP must be evaluated further to reduce the readmission.

Keywords: clinical pathway, COPD exacerbation

INTRODUCTION

The main objective of implementing the clinical pathway is to select best practice patterns from a wide variety of practice patterns, establish expected standards regarding the length of care and use of clinical procedures. In addition, the implementation of clinical pathways can be used to assess the relationship between various stages and conditions different in a process and develop strategies to produce faster services with fewer stages.[1,2]

Chronic Obstructive Pulmonary Diseases (COPD) exacerbation are

characterized by acute patient symptoms such as shortness of breath (dyspnea), cough, and/or purulent sputum, which may improve with routine medication. *The GOLD Report* 2014 explains that the cost for health due to COPD is 56% of the total cost to be paid for respiratory diseases. The highest costs are caused by the incidence of exacerbations of this disease.[3] The incidence of this disease increases with increasing age and is higher in men (4.2%) than in women (3.3%).[4]

METHOD

The type of this research is quantitative with survey analytic method and cross-sectional.[5] This research was conducted retrospectively and analyzed descriptively, namely the method of problem-solving which was investigated by describing the current state of the subject or research object based on visible facts or as they are. The medical record of Goenawan Partowidigdo Pulmonary Hospital (RSPG) files used in this study was from the beginning of 2019 to July 2020. The materials used were notes or data on the medical record card taken from RSPG Cisarua which is related to COPD. The data collection technique used a documentation study of 304 medical record files and clinical pathway (CP) forms.

The samples for COPD patients with the implementation of clinical pathways were 152 medical record files and for COPD patients without the implementation of the CP were 152 medical record files. The data analysis method used in this research is quantitative analysis. The hospital outcome analysis was in the form of Length of Stay (LOS) using Mann-Whitney, while the readmission rate (RR) and in-hospital mortality (IHM) used chi-square. Analysis of the outcome of the economy in the form of the total real costs of the two groups using Mann-Whitney.

RESULT

The results of the statistical analysis of the Mann Whitney difference test were obtained, which showed a very significant difference between the LOS with the CP method with LOS non-CP (P=0.0001). The results of the analysis showed that the average LOS for class 1 using CP was 3.64 days, 1.94 days more efficient than non-CP. Other parameters are IHM and RR, the results of the analysis of the two groups showed P>0.05, this indicates that there was no significant difference between the two groups.

The average total hospital rate per patient is relatively the same and does not show a statistically significant difference between the two clinical methods (Table 2.) However, in the RS rate variable, there is a significant difference between the CP and non-CP methods (P=0.0001). The average hospital rate using the CP method were Rp 1.693.753,00 for each patient.

Likewise, the average rates of nursing, radiology, accommodation rooms and drugs using CP are significantly more efficient than non-CP. The average efficiency obtained in the nursing, radiology, accommodation room and

medicine variables were Rp. 318,373,00, Rp. 27,717,00, Rp. 698,642,00 and Rp. 317,286,00 per patient.

Table 1. Comparison Results of Hospital Outcomes in Class 1 Inpatients with Exacerbation of COPD Cases in RSPG with CP and Non-CP in 2019

Outcome RS	Mean		P
	CP	Non CP	
LOS	3,64	5,58	0,0001**
IHM	0 (0%)	0 (0%)	0,277*
RR	6 (54,5%)	5 (45,5%)	0,539*

Note:
*Chi Square Test of significance 0,05
**Mann-Whitney Test of significance 0,05
LOS = Length of Stay; IHM = In-Hospital Mortality; RR = Readmission Rate

From Table 3, the statistical analysis results are obtained. Mann Whitney difference test, which shows a significant difference between the length of stay (LOS) with the CP and non-CP (P=0.0001). The results of the analysis show that the average LOS for class 2 using CP is 3.95 days, 1.65 days more efficient than non-CP. Other parameters are IHM and RR, the results of the analysis of the two groups showed P>0.05, this indicates that there was no significant difference between the two groups.

The RS rate variable has a significant difference between the CP and non-CP methods (P=0.002). The average hospital rate using the CP method can be streamlined as much as Rp. 1,086,813,00 per patient. The average efficiency obtained in the nursing variable, accommodation room and medicine, each of Rp. 208,285,00, Rp. 516,304,00 and Rp. 418,964,00 per patient.

Table 3. Comparison Results of Hospital Outcomes in Class 2 Inpatients with Exacerbation of COPD Cases in RSPG with CP and Non-CP in 2019 to 2020

Outcome RS	Mean		P
	CP	Non CP	
LOS	3,95	5,60	0.0001**
IHM	1 (100%)	0 (0%)	0,317*
RR	5 (62,5%)	3 (37,5%)	0,315*

Note:
*Chi Square Test 0.05 significance
**Mann-Whitney Test significance 0,05
LOS = Length of Stay; IHM = In-Hospital Mortality; RR = Readmission Rate

Table 5 showed the significant difference between the LOS with the CP method and non-CP. The results of the analysis show that the average length of time treated (LOS) for class 3 using CP is 4.12 days, 1.48 days more efficient than non-CP. Other parameters are IHM and RR, the results of the analysis of mortality rates for the two groups showed that there was no significant difference between the two groups.

Table 5. Comparison Results of Hospital Outcomes in Class 3 Inpatients with Exacerbation of COPD Cases in RSPG with CP and Non-CP in 2019 to 2020

Outcome RS	Mean		P
	CP	Non-CP	
LOS	4.12	5,58	0.000**
IHM	0 (0%)	0 (0%)	0,317*
RR	39 (70,9%)	16 (29,1%)	0,001*

Note:
*Chi Square Test 0.05 significance
**Mann-Whitney Test significance 0,05
LOS = Length of Stay; IHM = In-Hospital Mortality; RR = Readmission Rate

While the results of repeated analysis of patients from two groups showed P<0.05, this indicates that there was a significant difference between the two groups.

Table 2. Comparison Results of Economic Output in Class 1 Inpatients with Exacerbation of COPD Cases in RSPG with CP and Non-CP in 2019 to 2020

Variable	Mean		Mann-Whitney Statistical Value	P
	CP (N=25)	Non-CP (N=29)		
Total Tariff / INA CBGs (Rp)	7.248.008	7.066.041	303.50	0.292
Hospital Rates (Rp)	4.018.783	5.712.536	158.00	0.000
Non-Surgical Procedure (Rp)	14.400	10.344	360.00	0.895
Surgical Procedures	0	0	362.50	1.000
Experts	1.680	0	333.50	0.124
Nursing	617.920	936.293	237.50	0.030
Support	18.400	17.448	356.50	0.901
Radiology	104.800	132.517	250.50	0.037
Laboratory	485.360	510.465	358.00	0.938
Rehabilitation	27.600	82.241	273.50	0.066
Accommodation Room	782.000	1.480.642	129.00	0.000
Drug	1.540.444	1.857.730	246.00	0.043
BMHP	36.728	88.629	324.00	0.497
Difference in Fare	3.229.224	1.353.505	181.00	0.002

Table 4. Comparison Results of Economic Outcomes in Class 2 Inpatients with COPD Exacerbations in RSPG with CP and Non CP in 2019 to 2020

Variable	Mean		Mann-Whitney Statistical Value	P
	CP	Non-CP		
Total Tariff / INA CBGs (Rp)	5.749.135	6.211.465	201.00	0.469
Hospital Rates (Rp)	3.449.298	4.536.111	104.00	0.002
Non-Surgical Procedure (Rp)	0	0	230.00	1.000
Surgical Procedures	0	0	230.00	1.000
Experts	1.000	2.608	211.50	0.371
Nursing	452.475	660.760	137.00	0.024
Support	69.950	29.086	181.00	0.195
Radiology	123.350	113.913	219.00	0.766
Laboratory	549.025	542.826	208.50	0.601
Rehabilitation	28.250	69.782	190.00	0.252
Accommodation Room	500.000	1.016.304	68.50	0.000
Drug	1.118.612	1.537.576	149.00	0.049
Medical equipment	135.237	85.860	149.00	0.045
Difference in Fare	2.299.837	1.675.354	170.00	0.144

Table 6. Comparison Results of Economic Outcomes in Class 3 Inpatients with COPD Exacerbations in RSPG with CP and Non CP in 2019 to 2020

Variable	Mean		Mann-Whitney Statistical Value	P
	CP	Non-CP		
Total Tariff / INA CBGs (Rp)	4.727.407	5.122.443	435.10	0.018
Hospital Rates (Rp)	2.842.839	3.797.202	317.20	0.000
Non-Surgical Procedure (Rp)	8.971	1.440	530.25	0.594
Surgical Procedures	0	0	535.50	1.000
Experts	626	560	528.90	0.654
Nursing	446.476	624.065	367.60	0.000
Support	25.794	26.300	504.00	0.418
Radiology	74.018	66.700	532.00	0.939
Laboratory	315.757	385.785	452.00	0.057
Rehabilitation	18.317	19.780	533.90	0.971
Accommodation Room	322.429	439.000	354.00	0.000
Drug	1.127.951	1.613.050	325.00	0.000
Medical equipment	95.323	158.504	463.10	0.093
Difference in Fare	1.884.568	1.325.241	435.00	0.021

Table 6 shows the average total hospital rate per patient showed a significant between the two groups, and the RS rate variable also has a significant difference between the CP and non-CP methods. Meanwhile, the average hospital rate using the CP method can be streamlined as much as Rp. 954,363,00 per patient.

Case analysis of patients in the inpatient room class 3 in 2019 to July 2020, was carried out on 17 variables, with an average of nursing variables, accommodation rooms, drugs and difference in rates which showed a significant difference between CP and non-CP.

Likewise, the average nursing rates, accommodation rooms and drugs using CP are significantly more efficient than non-CPs. The average efficiency obtained in the nursing variable, accommodation room and medicine, each of Rp. 177,589,00, Rp. 116,571,00 and Rp. 485,099,00 per patient.

DISCUSSION

In this study, we compared the results (LOS, RR and IHM) of patients treated using CP and non-CP from medical record data from 2019 to 2020. This study proves the hypothesis that the use of CP in the management of COPD exacerbation reduces the duration of hospitalization (LOS). We found a significant reduction in LOS in the CP group compared to the non-CP group in inpatients class 1, 2 and 3. The overall mean LOS of exacerbated COPD patients using CP was 4 days while the overall mean LOS of exacerbated COPD patients who did not use CP is 6 days. A study by Andrea et al., who utilized exacerbation of COPD, also showed a significant reduction in the mean length of stay of 5 days in the CP group and 7 days in the non-CP group.[6] The same study was also conducted by Santamaria showing efficiency of 0.89 days (13.2%) of staying in the hospital using CP.[7] A retrospective study by Celis et al. (2011) also showed a significant decrease in LOS.[8]

This suggests that the implementation of CP can reduce the length of stay for patients in the hospital. and will also directly reduce the cost of care. Several things that cause the LOS value in patients to belong include age, disease severity and the presence of comorbidities.[9] These data are insufficient to demonstrate the optimal duration of hospitalization in patients with exacerbation of COPD. A study on the length of hospital stay required for COPD exacerbation was conducted by Mushlin *et al*. found that 6.9 days was considered the mean LOS.[10] The mean LOS that the investigators found was considered effective and efficient because it was past the average recommended antibiotic use period (3 to 7 days) of the GOLD guideline.[11] This study shows that treating exacerbated COPD patients using CP can help reduce the length of stay and indirectly reduce patient care costs.

Another parameter is IHM. The results of the analysis of the two groups showed that there was no significant difference between the two groups. There

was only one patient death in the CP group, namely in the class 2 patient and there was no death in class 1 and 3 in both the CP and non-CP groups. The risk of death in the hospital was independently associated with patient-related factors such as age, presence of respiratory acidosis and CCI.[12] COPD will have a negative impact on the quality of life of patients, including patients aged >40 years will cause the sufferer's disability. Even though they are still in the productive age group but cannot work optimally because of chronic shortness of breath. Comorbidity of COPD will result in cardiovascular disease, bronchial cancer, lung infections, thromboembolism disorder, asthma, hypertension, osteoporosis, joint pain, depression and anxiety.[13]

COPD mortality is higher in males and will increase in the >45 years age group. This could be attributed to decreased respiratory function at the age of 30-40 years 29. Research in America states that COPD is associated with a risk of death which is defined as the hazard ratio (HR).[13] Apart from the death of the patient in the hospital during treatment, the clinical outcome analyzed was the RR. Researchers did not find a significant difference in recurrent patient admission or RR between the two groups in class 1 and 2.

Whereas RR in grade 3 patients showed a significant difference between the CP and non-CP groups. The results showed that the most RR was in the CP group, both in grade 1, 2 and 3. As many as 6 patients (54.5%) in class 1, 5 patients (62.5%) in grade 2 and 39 respectively. patients (70.9%) were in grade 3. The main reason for re-entry in this study was shortness of breath.[6] The factors that cause the number of patients to return to the hospital are due to the presence of single or multiple comorbidities, inadequate therapy in the CP group patients, the comparison of the number of specialist doctors with the number of exacerbated COPD patients and the inadequate management of COPD exacerbations, for example, such as treatment of patients that have not been completed.[14]

The mean total hospital rates per patient showed a significant difference between the two clinical methods in both grades 1, 2 and 3 ($P<0.05$). In addition, the RS rate variable also has a significant difference between the CP and non-CP methods, with a significance value $P<0.0001$. The average hospital rate using the CP method can be streamlined as much as Rp. 1,693,753,00 per patient in class 1, Rp. 1,086,813,00 per patient in class 2 and Rp. 954,363,00 per patient. With these results, it can be concluded that the application of CP can reduce the cost of treatment.[2]

Another reason related to the implementation of the clinical pathway is the implementation of the National Health Insurance (Jaminan Kesehatan Nasional/JKN) system that has been implemented since January 2014 by the Health Insurance Management Agency (Badan Penyelenggara Jaminan Sosial/BPJS) using the Indonesian Cased Based Groups (INA-CBGs) tariff. The application of the tariff for the INA CBGs

package requires hospital management to be able to save costs and optimize hospital financial management, as well as carry out quality control, cost control and access through calculating the cost of care based on the calculation of unit costs owned by the hospital.[2] Implementation of CP is an interesting discussion among health workers.

The results of other studies show that there is budget efficiency (cost reduction) after the implementation of clinical pathways.[15] This is in line with the review of several studies conducted by Rotter et al., the result is that the implementation of clinical pathways can reduce treatment costs by up to $US 261 from ordinary care (without clinical pathways).[16]

Some of the advantages of implementing the *clinical pathway* are the uniformity of services and the ease with which the health staff team manages patients. In developed countries such as the UK, America and Australia *clinical pathways* continue to be developed and have a positive impact on the quality of life of patients, cost efficiency and minimize variations in action. The variations that occur can be in the form of variations in action or variations in the use of drugs.[17]

CONCLUSION

There are differences in clinical outcomes before and after the implementation of clinical pathways in the treatment of exacerbation COPD disease. The difference in the overall mean length of stay of exacerbated COPD patients using CP was 4 days while the overall mean LOS of exacerbated COPD patients who did not use CP was 6 days. *In-Hospital Mortality* (IHM) there was only one patient death in the CP group, namely in the class 2 patient and there were no deaths in class 1 and 3 in both the CP and non-CP groups. As for the *Readmission Rate* (RR), the results of the study showed that the most RR was in the CP group, both in grade 1, 2 and 3 patients. 6 patients (54.5%) respectively in class 1, 5 patients (62.5 %) in class 2 and 39 patients (70.9%) in class 3. The average total hospital rate per patient shows a significant difference between the two clinical methods in both classes 1, 2 and 3. In addition, the RS rate variable also has a significant difference between the CP and non-CP methods.

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Original Article

Accuracy Between CURB-65 Score and PSI in Determining The Prognosis of Community-Acquired Pneumonia Patients at H. Adam Malik General Hospital, Medan

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Abstract

Background: Community-Acquired Pneumonia (CAP) is an important problem associated with morbidity and mortality. An accurate initial assessment is required before starting management of a CAP patient to determine the prognosis of the patient as early as possible. The CURB-65 score and PSI (Pneumonia Severity Index) are initial assessment scores that can be used. This study aimed to compare the accuracy between the CURB-65 score and the PSI in determining the prognosis in CAP patients at H. Adam Malik General Hospital Medan.

Method: A descriptive study was conducted on 76 patients diagnosed with CAP. Each patient was assessed for their CURB-65 score, PSI class and mortality within 30 days of admission. Data were collected through patient medical records diagnosed CAP in 2018 and performed statistical analysis using 2x2 tables.

Results: The CURB-65 ≥3 score showed accuracy (71.0%), sensitivity (53.8%), and specificity (89,2%). The CURB-65 ≥ 2 score showed accuracy (75.0%), sensitivity (82.1%), and specificity (67.6%). Meanwhile, the Class IV-V PSI showed accuracy (77.6%), sensitivity (87.2%) and specificity (67.6%).

Conclusion: The accuracy of the PSI is higher when compared to the CURB-65 score in determining the prognosis of CAP patients at H. Adam Malik General Hospital Medan. Although PSI is more accurate, CURB-65 is simpler, easier and less expensive to use.

Keywords: CURB-65, PSI, accuracy, prognosis, community-acquired pneumonia

INTRODUCTION

Community-Acquired Pneumonia (CAP) is an important problem associated with morbidity and mortality.[1] CAP is an acute, community-acquired inflammation of the lung parenchyma.[2] CAP occurs in 3-5 cases per 1000 people each year, especially in the elderly with a 10-fold increase in incidence.[1] In the United States, pneumonia is the leading cause of death

associated with infections with potentially serious complications such as respiratory failure and sepsis.[3] Every year in the United States (US) an average of 5 to 6 million people suffer from CAP, and more than 1 million of them require hospitalization. About 10-20% of patients suffering from CAP need to be admitted to the Intensive Care Unit (ICU), and about 20-50% of them eventually die.[4] In Japan, Community Pneumonia is the 4th cause of death. In Indonesia, pneumonia is included in the top 10 inpatient diseases at the hospital.[2]

Table 1. Components of Pneumonia Severity Index (PSI)[2]

Characteristics	Score
Demographic factors	Age (years)
Demographic factors	Age (years)
Men	– 10
Women	+ 10
Nursing home resident	
Coexisting illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Findings on physical examination	
Altered mental status	+20
Respiratory rate⩾30/min	+20
Systolic blood pressure <90 mm Hg	+20
Temperature<35°C or ⩾40°C	+15
Pulse ⩾125 beats/min	+10
Laboratory and radiographic findings	
pH <7,35	+30
BUN >10.7 mmol/L or BUN >29 mg/dL	+20
Sodium <130 mEq/L	+20
Glucose >13.9 mmol/L or Glucose >250 mg/dL	+10
Haematocrit <30 %	+10
The partial pressure of arterial oxygen <60 mm Hg	+10
Pleural effusion	+10

Each variable has its score and is calculated into 5 classes as in (Table 2).[2] Although PSI has a high discriminatory value, the calculation is complex, difficult to use in a hospital with inadequate facilities and infrastructure and ignores disease severity in young patients without comorbidities.[5]

Table 2. Total score of PSI in Severity Risk Class[2]

Severity Risk Class	Total Score of PSI
I	≤50
II	51-70
III	71-90
IV	91 - 130
V	>130

Whereas CURB-65 is a simpler clinical score than PSI because it only uses five variables (Table 3).

Table 3. Components of CURB-65 Score[2]

Characteristics	Score
Confusion	1
Urea >7 mmol/L or Blood Urea Nitrogen (BUN) >19 mg/dL	1
Respiratory Rate ≥30/minute	1
Blood pressure (Systolic <90 mmHg or Diastolic ≤60 mmHg)	1
Age ≥65 years old	1

Confusion (defined as disorientation in people, time and place), urea (urea >7 mmol/L or BUN (Blood Urea Nitrogen) >19 mg/dL), respiratory rate (respiratory rate ≥30/minute), blood pressure (systolic <90 mmHg or diastolic ≤60 mmHg) and age (older than 65 years).[6]

Each scoring system has strengths and weaknesses. The PSI is well validated for identifying low-risk patients but may underestimate illness severity in young, otherwise healthy patients, due to the heavy weighting it accords to age and comorbidities. On the other hand, CURB-65 may better identify patients at the severe end of the spectrum, because it evolved from prediction rules originally designed to identify patients with severe CAP.

In the study of Michelle et al, it was said that the PSI score of class IV/V was better than CURB-65 ≥3 score in predicting patient mortality within 30 days.[7] Meanwhile, in a study conducted by Kim et al at 14 hospitals in Korea it was said that the 30-day mortality rate for CAP patients based on the CURB-65 score was more valid for lower scores, while the PSI score was more valid for higher scores.[8] This is in line with research conducted by Alavi-Moghaddam which concluded that the CURB-65 score is a more recommended method than the PSI score for predicting mortality in CAP patients.[9] So, this study aimed to compare the accuracy between the CURB-65 score and the PSI score in determining the prognosis in CAP patients.

METHOD

A cohort retrospective study was conducted on patients diagnosed with CAP. Data were collected from medical records of patients diagnosed with CAP from January–December 2018. Medical records were reviewed to confirm the diagnosis of CAP. The diagnosis of CAP in this study is based on the Indonesian Society of Respirology (ISR), a definite diagnosis of CAP is confirmed if there is an infiltrate/air bronchogram on the chest X-ray with any of the following symptoms or signs: cough, change in sputum/purulent characteristics, body temperature ≥38°C (axillary)/history of fever, chest pain, shortness of breath, on physical examination, there may be signs of consolidation, bronchial breath sounds and crackles, leukocytes ≥10,000 or ≤4500.

The sample in this study must meet the inclusion criteria and exclusion criteria. The inclusion criteria in this study were as follows: age more than 18 years, admission to the H. Adam Malik General Hospital from the emergency room and the patient was diagnosed with CAP by a Pulmonologist. The exclusion criteria in this study were as follows: patients with tuberculosis, patients with aspiration pneumonia, patients who have been hospitalized previously with a length of stay more than 48 hours before admission to H. Adam Malik General Hospital. Prognosis in CAP patients is measured using the short-term mortality rate. This short-term mortality rate is defined as death that occurs within 30 days of hospitalization.

A total of 76 patients met the inclusion and exclusion criteria in this study. Each patient was assessed for their CURB-65 score, PSI class and mortality within 30 days of admission. This study was performed statistical analysis using 2x2 tables for each PSI class and CURB-65 score. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy are measured and compared for each cut of point PSI Class and CURB-65 score. Sensitivity is expressed as the proportion of correctly classified as true positives mortality among

each cut of point CURB-65 score and PSI Class (TP/TP+FN). (TP=True Positive Value; FN=False Negative Values) Whereas specificity is expressed as the proportion of correctly classified as true negatives among the total non-mortality patients (TN/TN+FP). (TN=True Negative Value; FP=False Positive Values) The positive predictive value of test (PPV) is the probability of a study subject who has mortality when restricted to those subjects who had a positive test. It can be calculated as (TP/TP+FP). The negative predictive value of a test is the probability of a study subject who will not have mortality when restricted to those subjects who test negative. It can calculate as (TN/FN+TN). The accuracy of a test is expressed as the proportion of those individuals correctly categorized by the test (those with the disease who had a positive test plus those without the disease who had a negative test result). It can be calculated as (TP+TN/TP+FP+FN+TN).

This study has been approved by the Ethical Research Committee of the Faculty of Medicine, Universitas Sumatera Utara.

RESULT

A total of 76 patients were assessed in this study. The patients in this study met inclusion and exclusion criteria. The data showed that 42 patients (55.3%) are male and 34 patients (44.7%) are female. The age distribution of patients in this study was evenly distributed in all age groups. The distribution of age in this study could be seen in (Table 4). The majority The most common comorbidities in this study were hematological disorders such as anemia, thrombocytopenia, pancytopenia and bicytopenia. For comorbid diseases in this study can be seen in (Table 4).

Table 4. Demographic characteristics based on gender, comorbidity, age and education

Characteristics	n	%
Gender		
Male	42	55.3
Female	34	44.7
Age		
<40 years old	14	18.4
40 - 49 years old	13	17.1
50 - 59 years old	16	21.1
60 - 69 years old	18	23.7
≥70 years old	15	19.7
Comorbidity		
Respiration	9	11.8
Endocrine	17	22.4
Cardiology	25	32.9
Malignancy	11	14.5
Electrolyte Imbalance	30	39.5
Gastrointestinal Tract	15	19.7
Neurology	17	22.4
Nephrology	15	19.7
Hematology	31	40.8
Hipoalbumin	17	22.4
HIV	2	2.6
Urology	6	7.9
No Comorbidity	1	1.3
Education		
Primary School/No Education	18	23.7
Junior High School	19	25
Senior High School	30	39.5
College	9	11.8

The distribution of mortality within 30 days for each class of PSI and CURB-65 score can be seen in (Table 5). We can see that the higher the PSI class and the higher the CURB-65 score, the higher the mortality rate. There is a correlation between class of PSI and CURB-65 score with mortality within 30 days. The results of sensitivity, specificity, PPV, NPV and accuracy between the PSI class and the CURB-65 score are shown in (Table 6).

Table 5. Correlation between severity score and 30-d mortality

Severity Score	All Patient	30-d mortality		P
		Yes	No	
	n (%)	n (%)	n (%)	
PSI				
Class V	24 (31.6)	19 (48.7)	5 (13.5)	<0.001
Class IV	22 (28.9)	15 (38.5)	7 (18.9)	
Class III	18 (23.7)	3 (7.7)	15 (40.5)	
Class II	7 (9.2)	1 (2.6)	6 (16.2)	
Class I	5 (6.6)	1 (2.6)	4 (10.8)	
CURB-65				
5 points	1(1.3)	1 (2.6)	0 (0.0)	<0.001
4 points	8 (10.5)	8 (20.5)	0 (0.0)	
3 points	16 (21.1)	12 (30.8)	4 (10.8)	
2 points	19 (25)	11 (28.2)	8 (21.6)	
1 points	17 (22.4)	6 (15.4)	11 (29.7)	
0 points	15 (19.7)	1 (2.6)	14 (37.8)	
Total	76 (100.0)	39 (100.0)	37 (100.0)	

Table 6. Accuracy for predicting mortality

Severity Score	%Sensitifity	%Spesificity	%PPV	%NPV	%Accuracy
PSI					
Class V	48.7	86.5	79.1	61.5	67.1
Class IV-V	87.2	67.6	73.9	83.3	77.6
Class III-V	94.9	27	57.8	83.3	61.8
Class II-V	97.4	10.8	53.5	80	55.2
CURB-65					
=5 points	2.6	100	100	49.3	50
≥4 points	23.1	100	100	55.2	60.5
≥3 points	53.8	89.2	16	64.7	71
≥2 points	82.1	67.6	72.7	43.1	75
≥1 points	2.6	37.8	74.5	93.3	68.4

The highest accuracy in this study is in the PSI IV-V class with accuracy (77.6%), sensitivity (87.1%) and specificity (67.6%). The results for the CURB-65 ≥2 score showed accuracy (75.0%), sensitivity (82.1%), and specificity (67.6%). The results for the CURB-65 ≥3 score showed accuracy (71.0%), sensitivity (53.8%), and specificity (89,2%). That means that the PSI Class IV-V is more accurate in predicting mortality within 30 days of hospitalization.

DISCUSSION

The mortality of CAP in this study was 51.3% with a total sample of 76 patients (Table 1). This is not much different from the study conducted by Mortensen et al, where it was found that CAP mortality rate was 53% of the total study sample of 208 patients.[10] Whereas, in a study conducted by Zhang et al, with a larger sample of 3224 patients, the mortality rate associated with CAP was 15.7%.[11] The mortality rate obtained by Zhang et al is far different from that in this study because a larger sample size will represent the state of the population.

Lanks et al attempted to carry out an epidemiological study that identified risk factors for an increased incidence of CAP and found that the magnitude of the risk of CAP increased with increasing patient age and the presence of comorbidities. These comorbidities include chronic airway

diseases, such as chronic obstructive pulmonary disease and bronchiectasis, as well as non-respiratory problems such as cardiovascular and kidney disease.[12]

This relatively not much different from previous studies where almost all patients who were the subject of this study had comorbidities (Table 1). Only 1 patient had no comorbid disease. The most common comorbids found in this study were hematological disorders, 31 patients or 40.8% of the subjects. These hematological disorders can include anemia, thrombocytopenia, leukemia, and thrombosis. Another comorbid that is relatively common in this study is electrolyte disturbances which were found in 30 patients or as much as 39.5%. These electrolyte imbalances can include hyponatremia or hypokalaemia.

Every time the PSI class increases, and the CURB-65 score increases, the mortality rate will increase (Table 2). This is consistent with research conducted by Wiersinga et al, which showed that the mortality rate within 30 days increases when the CURB-65 score increases.[13] This is also consistent with research conducted by Kim et al, which showed that the mortality rate in 30 days increased when the PSI class increased.[8] So there is a correlation between the increase in the CURB-65 score and the PSI class with mortality within 30 days of hospitalization.

Sensitivity, specificity, PPV, NPV and accuracy between the PSI class and the CURB-65 score are shown in Table 3. The focus in this study is measuring accuracy, accuracy of a test is expressed as the proportion of those individuals correctly categorized by the test (those with each cut of point score who had a positive test (mortality within 30 days hospitalization) plus those undercut of point score who had a negative test result (no mortality within 30 days hospitalization). The accuracy PSI IV-V class in this study is 77.6%. The accuracy of the CURB-65 ≥3 score in this study was 71%, while the accuracy of the CURB-65 ≥2 score in this study was 75%. Therefore, in this study, it can be concluded that the highest accuracy is in PSI class IV-V. Another study that is in line with this study is a study conducted by Michelle et al It was said that the sensitivity of the PSI grade IV/V score was better than the CURB-65 score ≥3 in predicting patient mortality within 30 days (94% vs 62%).[7]

Another meta-analysis study conducted by Chalmers et al in 2010 attempted to analyze 33 cohort studies with 81,700 patients. This study compared the sensitivity and specificity levels of the PSI score. The study shows that the PSI score has a better level of accuracy compared to the CURB-65 score and the CURB-65 score, as evidenced by the larger PSI area under the curve (AUC) (82% vs 79%).[14] This PSI score has higher accuracy than the CURB-65 score because the PSI score uses 20 variables, but this score takes longer to collect data from these 20 variables when compared to the CURB-65 score which only uses 5 variables.

The limitation of this study is that this study is retrospective, there can be bias in the information obtained. Comorbid obtained from the final diagnosis of

patients who died or survived in this study patient may not represent all the comorbid present in these patients because some examinations have never been done before. Patients who survive in this study are patients who discarded for outpatient treatment, and there is no follow-up after the patient discarded, the patient discarded for outpatient treatment may go back to the hospital after discarded.

CONCLUSION

A severity score can be used to predict mortality within 30 days of a patient with CAP. The Result of Class IV-V PSI showed accuracy (77.6%), sensitivity (87.1%) and specificity (67.6%). The results for the CURB-65 ≥2 score showed accuracy (75.0%), sensitivity (82.1%), and specificity (67.6%). The results for the CURB-65 ≥3 score showed accuracy (71.0%), sensitivity (53.8%), and specificity (89,2%). The accuracy of class IV-V PSI is higher when compared to the CURB-65 ≥3 and CURB-65 ≥2 score in determining the prognosis of CAP patients at H. Adam Malik General Hospital Medan. Although PSI is more accurate, CURB-65 is simpler, easier and less expensive to use.

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Case Series

Remdesivir for COVID-19 in Indonesia: A Case Series

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Abstract

To date, COVID-19 still gives rise to a high mortality rate in Indonesia. The definitive therapy has yet to be found. However, some medications are said to be potential in subduing the infection, e.g. remdesivir. United States, Japan, and some countries in Europe had use remdesivir against severe COVID-19 infection. In Indonesia, no study has shown to discuss remdesivir therapy for severe COVID-19. This case series shows the first five remdesivir usages in severe COVID-19 patients in RSDC Wisma Atlet Kemayoran, Jakarta. In this retrospective case series, we include the first five severe COVID-19 patients that got remdesivir plus standard therapy in Rumah Sakit Darurat COVID-19 Wisma Atlet Kemayoran, Jakarta in October 2020. Five patients who got remdesivir in this case series experienced clinical and laboratory improvement. The ventilation and oxygenation status, as well as PF ratio and the neutrophils-lymphocytes ratio (NLR), got better. The possible side effect of remdesivir usage, renal function impairment, was not seen in these patients. At last, the five patients were discharged home with negative swab results, three until seven days after remdesivir therapy finished. Remdesivir therapy for COVID-19 in this case series is associated with a good outcome. Compassionate use of remdesivir should be considered in severe COVID-19. However, a bigger sample of randomized control trial needs to be done to show the effectiveness of remdesivir against COVID-19.

Keywords: GS-5734, SARS-COV-2, coronavirus

INTRODUCTION

COVID-19 infection is one of the major problems in the world. An increase in mortality and morbidity rate caused by this infection is still being reported to have a high number in some countries and associated with high severity from COVID-19 itself. Indonesia has a high Case Fatality Rate (CFR) compared with other Asia countries. In April 2020, CFR in Indonesia reaches 8.13%, followed by other countries such as the Philippines (6.66%), Myanmar (3.36%), and Thailand (1.84%).[1] It showed that the COVID-19 problem in Indonesia has not been resolved and still receives a 'bad report card' set against others.

Up until this day, definitive therapy has not been found. One of the antivirals that should be considered is remdesivir,

which is an adenosine analog class that was originally used in several viral infections such as a Respiratory syncytial virus (RSV), Nipah virus, ebola virus, and Marburg virus.[2] Remdesivir was used in coronavirus infections such as SARS-CoV-1 and middle east respiratory syndrome (MERS-CoV) and is effective and proved by in-vitro tests.[3,4] Remdesivir confirmed has half-life in 12 hours after the infection of MERS-CoV and inhibit lung damaged. Remdesivir acts on the RNA-dependent RNA polymerase (RdRp) structure in the virus, furthermore inhibits the replication of the SARS-CoV- 2 virus in the airway epithelial cells.[5]

Several countries are already using remdesivir as a therapy for COVID-19. Remdesivir usage in the USA has been authorized by the US Food & Drug Administration.[6] Comparable things were done by Japan in patients with severe COVID-19 conditions based on the preliminary phase 3.[7] Based on data reported by research on 500 subjects divided into healthy groups infected with the acute ebola-virus, remdesivir has a safe clinical profile.[8] Indonesia has not yet had a preliminary report regarding the use of remdesivir as an antiviral, especially in the case of COVID-19. In this case series, a further description of COVID-19 patients who received remdesivir therapy was described.

METHOD

This case series is a retrospective study by collecting all patients who received remdesivir therapy within 5 and 7 days at the Emergency Hospital for COVID-19 Wisma Atlet Kemayoran Jakarta in October. The patient is admitted to the High Care Unit (HCU) with Acute Respiratory Distress Syndrome (ARDS) confirmed by Berlin Definition criteria, with or without comorbid or weighting factors. Patients receiving remdesivir were monitored daily from the start to the end of their HCU treatment and thereafter continued monitoring in the ward until the patient was discharged. Administration of remdesivir was followed by administration of standard therapy that had been determined in the hospital as well as additional therapy that was given based on the clinical situation in each patient

RESULT

All the 5 cases hospitalized status from the start of admission to the emergency room, receiving remdesivir therapy until the patient is discharged can be seen in Figure 1. Table 1 shows case's background, assessment, and therapy received during treatment. Table 2 and Figure 2 illustrate the ventilation and oxygenation status, as well as clinical parameters of cases before and after receiving remdesivir therapy.

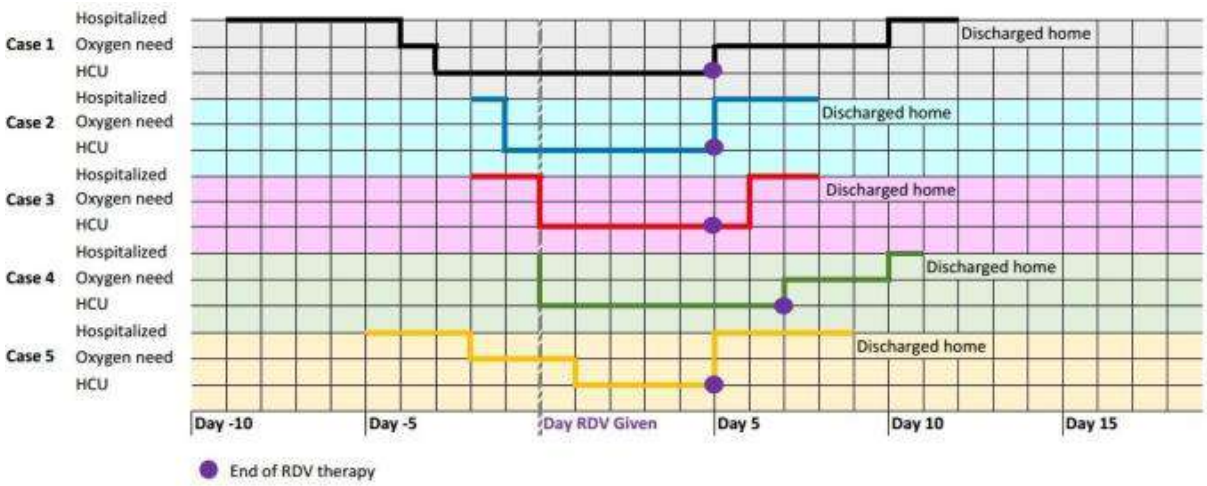

Figure 1. Timeline of confirmed COVID-19 patients who got remdesivir therapy

Table 1. Patient background, assessment and medications

	Case 1	Case 2	Case 3	Case 4	Case 5
Patient's background					
Age (Years old)	64	46	33	43	61
Gender	Male	Male	Male	Male	Male
Symptoms on admission	Headache	Cough, fever, fatigue	Nausea, vomiting, stomachache, loss ofappetite, fever	Nausea, vomiting, lossof appetite, dysgeusia	Cough, fever
BMI (kg/m^2)	27.8	25.6	27.5	27.1	22.7
Comorbidity	Absent	Absent	Absent	Absent	Diabetes Mellitus
Assessment					
Assessment on admission	Confirmed Covid-19 with mild symptom	Confirmed Covid-19 with moderate symptom	Confirmed Covid-19 with mild symptom	Confirmed Covid-19 with moderate symptom	Confirmed Covid-19 with mild symptom
Assessment on HCU	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom
Adverse Events	Severe ARDS Respiratory alkalosis Pneumonia Bilateral Elevated Liver Enzyme Electrolit Imbalance	Mild ARDS Ischemic Heart DiseaseElevated Liver Enzyme Dyslipidemia Deltoid hematoma	Mild ARDS Elevated Liver Enzyme Deltoid Hematome Deltoid, Heparin-Induced Thrombocytopenia	Moderate ARDS Respiratory alkalosis Pneumonia Bilateral Elevated Liver Enzyme	Moderate ARDS Respiratory alkalosis Hypertension Left pleural effusionAKI Elevated Liver Enzyme
Medications					
Antiviral	Oseltamivir, Remdesivir	Remdesivir	Remdesivir	Remdesivir	Oseltamivir, Remdesivir
Antibiotic	Azithromycin, Levofloxacin, Cefoperazone Meropenem	Ceftriaxone, Cefixime	Moxifloxacin, Ceftriaxone	Cefotaxime, Moxifloxacin, Meropenem, Cefepime	Azithromycin, Ceftriaxone, Moxifloxacin, Cefepime
Corticosteroids	Dexamethasone	Methylprednisolone	Methylprednisolone	Methylprednisolone, Dexamethasone	Dexamethasone
Anticoagulant	Heparin	Fondaparinux	Heparin	Heparin	Heparin

Figure 2. Patients' laboratory parameter before and after Remdesivir therapy

Table 2. Patient ventilation and oxygenation status before, during and after Remdesivir therapy

Before Remdesivir Therapy				Day of Remdesivir Therapy							Day After Remdesivir Therapy		
Case number		**Day of HCU admission**	**Day of Remdesivir therapy**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**Clinical outcome**
Ventilation and Oxygenation													
1	Time vs Remdesivir	5 d after adm	5 d after										D 5 post Remdesivir remains. In hospital onward with NC 2 lpm
	O_2 delivery method	NRM		HFNC	HFNC	HFNC	NRM	NRM			NRM	NRM	
	FiO_2 (%)	100		60	50	50	100	100			80	60	
	PF *ratio* (mmHg)	181.75		165	60	166	198	161			175	233	Discharged home D7 post Remdesivir
	SpO_2 (%)	96		98	98	98	97	96			96	97	
2	Time vs Remdesivir	2 d after adm	1 d after										Discharged home D 3 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	37		33	33	21	21	21			21	21	
	PF *ratio* (mmHg)	218		290		466		466			471		
	SpO_2 (%)	98		98	98	98	98	99			98	98	
3	Time vs Remdesivir	2 d after adm	Same day										Discharged home D 3 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	37		34	33	21	21	21			21	21	
	PF *ratio* (mmHg)	262		291		471		466			466		
	SpO_2 (%)	98		98	99	99	99	99			99	99	
4	Time vs Remdesivir	Same day	Same day										Discharged home D 4 post Remdesivir
	O_2 delivery method	NRM		HFNC	HFNC	HFNC	NRM	CPAP	NRM	NC	NC	NC	
	FiO_2 (%)	100		70	55	55	100	65	100	40	37	29	
	PF *ratio* (mmHg)	309		164	342.7	180	176.9	169	323	245	275	341	
	SpO_2 (%)	99		99	98	98	97	98	98	98	95	96	
5	Time vs Remdesivir	5 d after adm	5 d after										Discharged home D 4 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	29		29	29	21	21	21			21	21	
	PF *ratio* (mmHg)	476		277		457		452			461		
	SpO_2 (%)	98		98	98	97	98	99			99	99	

Case 1

A 64-year-old male patient came to the hospital complaining of a headache. The patient was treated in the ward with standard COVID-19 therapy in the form of Oseltamivir, Azithromycin, Vitamin B Complex, Zinc. On the 6th day of treatment, the patient was transferred to HCU due to desaturation by SpO_2 of 89% with room air, the presence of moderate ARDS and bronchopneumonia. During the HCU treatment, the patient experienced desaturation with SpO_2 of 85% with non-rebreathing mask (NRM) 15 lpm and a respiration rate of 36 times per minute in the presence of severe ARDS so that oxygen therapy was changed into high flow nasal canule (HFNC) Flow 40 FiO_2 90% and was replaced with CPAP PEEP 5 mbar FiO_2 70% after the condition was improved.

Patients received antibiotic therapy in the form of Azithromycin, Levofloxacin, Cefoperazone and Meropenem. Remdesivir 2x100 mg was given on day 6 of treatment in HCU and continued 1x100 mg for 5 days. The patient received heparin therapy while in HCU. The patient was admitted in HCU for 15 days, then transferred to the ward with a saturation of 98% using 2 lpm nasal canule. On the 22nd day of treatment, the PCR results were negative and the patient was discharged.

Case 2

A 46-year-old male patient came to the hospital with a cough, sore throat and a history of fever since 4 days before admitted to the hospital. The patient was transferred to the HCU on the 2nd day due to a decrease in SpO_2 of 92-93% with room air and the presence of mild ARDS. During HCU treatment, the patient was given 4 lpm nasal canule oxygen therapy with a saturation of 98-99%. The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The patient was allergic to moxifloxacin and meropenem, so he was given antibiotic therapy in the form of ceftriaxone.

The patient received fondaparinux therapy for 4 days then discontinued it due to hematoma in the right arm. This condition occurred 1 day after the pain and heavy breathing. The patient was treated in HCU for total of 5 days, on the 6th day of treatment the patient did not complain of coughing and sore throat, the hematoma in the right arm become better so that the patient was transferred to a ward with SpO_2 of 99% with room air. On the 10th day of treatment, PCR results were negative and the patient was discharged.

Case 3

A 33-year-old male patient came to the hospital complaining of vomiting more than four times, headache, weakness and a history of fever 2 days before he was hospitalized. The patient had taken Oseltamivir 2x75 mg and Azithromicyn 1x500 mg for 5 days before coming to the emergency room. Patients are treated in the ward and receive standard COVID-19 therapy. On day 2 of the treatment patient was transferred to HCU due to worsening of the patient's condition accompanied with desaturation of SpO_2 by 95% with room air

and mild ARDS. During HCU treatment, the patient was given 4 lpm nasal canule with SpO2 of 98-99%. The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The combination of antibiotics given in HCU is Moxifloxacin and Ceftriaxone. Patients received heparin therapy while being treated in HCU, on the third day of treatment the heparin was changed to 10,000 IU drip depleted in 2 hours. At 2 hours of administration of heparin drip, the patient complained of a hematoma on the left arm.

Complete blood count and coagulant factors were carried out and the results of thrombocytopenia ($87x10^3$/uL) and an increase in D-Dimer (814 ng/mL) were performed without other bleeding complaints such as nosebleeds, bleeding gums, and melena, then the patient was diagnosed with Hematoma due to Heparin-Induced Thrombocytopenia (HIT). Heparin was stopped, and the patient was given heparin sodium gel and warm compresses to the area of the hematoma. The patient was admitted to the HCU for a total of 5 days, on the 6th day of treatment at the HCU the patient had no complaints of nausea, vomiting, and headaches, the hematoma in the left arm had improved so that the patient was transferred to the ward with SpO_2 of 99% room air. On the 10th day of treatment, PCR results were negative and the patient was discharged.

Case 4

A 43-year-old male patient came to the hospital with complaints of dysgeusia and dry cough 5 days before admitted to the hospital. At the time of examination in the ER, the patient's respiration rate was 28 times per minute with SpO_2 of 89% room air, moderate ARDS and Bilateral Pneumonia. The patient was immediately transferred to HCU. During HCU treatment, oxygen therapy was replaced from NRM 15 lpm into HFNC Flow 30 FiO_2 70%. On the 5th day of treatment, the patient still complaining of shortness of breath accompanied by a productive cough. HFNC was changed into NRM 15 lpm with SpO_2 of 97%. On the 6th day of treatment, the symptoms were getting worse, so that the oxygen therapy was changed to CPAP 6 mbar FiO_2 65%. On the 7th day of treatment, the CPAP oxygen therapy was changed to NRM 15 lpm with SpO_2 of 98%. On the 8th day of treatment oxygen therapy was changed to a 5 lpm nasal canule with SpO_2 of 95%. On the 10th day of treatment, the complaints of shortness of breath and cough were reduced with SpO_2 of 95% with 2 lpm nasal canule.

Remdesivir was given 2x100 mg on the first day of treatment in HCU, followed by 1x100 mg for 5 days and continued for 7 days in consequence of patient deterioration condition. The combination of antibiotics given is cefotaxime, moxifloxacin, meropenem and cefepime. The patient received heparin therapy during his HCU stay. The patient was admitted to the HCU for a total of 10 days. On the 10th day of treatment, the patient did not complain of coughing and shortness of breath, so the patient was transferred to the ward with SpO_2 of 95% using a 3 lpm nasal

canule. On the 14th day of treatment, PCR results were negative and the patient was discharged.

Case 5

A 61-year-old male patient came to the hospital with complaints of fever for 9 days accompanied by cough and runny nose. The patient had a history of Diabetes Mellitus and Hypertension. Patients are treated in the ward with standard therapy. On day 6 of treatment, the patient experienced desaturation by SpO_2 of 95% room air accompanied by Mild ARDS with left pleural effusions so that the patient was transferred to HCU. During the HCU treatment, the patient was given oxygen therapy in the form of 2 lpm Nasal Canul with SpO_2 of 98-99%.

The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The combination of antibiotics given at HCU is azithromycin, ceftriaxone, moxifloxacin. The patient received heparin therapy during his HCU stay. The patient was admitted to the HCU for 5 days. On the 6th day of treatment at the HCU, the patient did not complain of coughing, so the patient was transferred to a regular treatment room with 99% saturation of room air. On the 14th day of treatment, PCR results were negative and the patient was discharged.

DISCUSSION

This case series describes the first five severe COVID-19 patients who got remdesivir therapy in RSDC Wisma Atlet Kemayoran, Jakarta. It is a retrospective, uncontrolled, and open-label study. However, this study needs to be published to show the potency of remdesivir against COVID-19, particularly in Indonesia.

United States Food Drug Administration released the Emergency Use Authorization (EUA) for emergency use of remdesivir in Mei 2020. Remdesivir therapy is allowed for adults and children with severe COVID-19 confirmed by PCR swab, and severe symptoms are showed by oxygen saturation below 94% on room air, require oxygen therapy, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) in high intensive care unit (HCU) setting.[1]

Remdesivir is pharmacologically effective against several viral infections. Remdesivir acts as a monophosphate nucleotide analog inside cells. It alters the monophosphate structure to nucleoside triphosphate, later it will be the adenosine triphosphate (ATP) analog. This structure will compete against ATP substrate to inhibit the RNA-dependent RNA polymerase of the virus, and consequently, the virus replication process will be slow down.[2]

Remdesivir was found to be effective against MERS-CoV and SARS-CoV-1 according to in vitro studies.[3–5] A better outcome was obtained by combining remdesivir with interferon beta group medication and lopinavir-ritonavir.[3]

Some studies have shown the efficacy of remdesivir against COVID-19 and related viral infection. A case report

from Washington, USA demonstrated progressive clinical and radiological improvement of the patient with pneumonia after 7 days of remdesivir therapy. Besides remdesivir, vancomycin and cefepime were also given.[4] In-vitro trial using vero cells showed that remdesivir was effective in inhibiting SARS-CoV-2 infection.[5] Another study showed that the active agents of remdesivir could reduce the viral load in the bronchoalveolar lavage sample and lung infiltrate in the rhesus macaque model.[6] A study by Pizzorno *et. al.* demonstrated SARS-CoV-2 replication is inhibited by remdesivir on the respiratory cell of bronchus and nasal.[7] A double-blind randomized control trial study found that COVID-19 patients who got remdesivir were recovered faster compared to the placebo group (P<0.001).[8] Our case series showed that clinical and laboratory improvement was achieved by five patients after remdesivir therapy combined with antibiotics, anticoagulants, corticosteroids, antioxidants, and vitamins.

A randomized control trial study by the National Institute of Allergy and Infectious Diseases (NIAID) on 1063 COVID-19 patients from February until April 2020 compared time to clinical improvement of remdesivir group and placebo group. Clinical improvement was achieved within 11 days in remdesivir group, while the placebo group 15 days.[8]

Another open-label, randomized, and phase 3 study by Gilead Science compared clinical improvement of severe COVID-19 patients who got 5 and 10 days of remdesivir therapy. Fourteen days after the first remdesivir therapy, clinical improvement was evaluated and insignificant outcomes were obtained (Odds Ratio=0.75; 95% CI=0.51-1.12). Some 60% of the patients in 5 days remdesivir group were discharged home on day 14, while 10 days group was 52.3%. Early remdesivir therapy within 10 days after symptoms appeared resulting in clinical improvement of 62% of the patient on day 14 of hospitalization.[2]

The five patients in our case series got remdesivir therapy within 10 days after admitted to the hospital. Good clinical outcomes were seen in these patients as well as the short length of hospital stay. The longest stay was 21 days, while the shortest was 10 days. The patient with the shortest length of stay got remdesivir on his second day of hospitalization, while the longest got remdesivir on his ninth day of hospitalization.

One of the inflammatory markers that is known as a prognostic factor for pneumonia is the neutrophil-lymphocyte ratio (NLR).[9] Neutrophils are one of the leukocyte components that appears when inflammatory factors, such as IL-6, IL-8, TNF, and IGF are released, consequently induce reactive oxygen species (ROS) formation and DNA damages. Meanwhile, CD4+ T lymphocyte will decrease and CD8+ suppressor T lymphocyte will increase in systemic inflammation caused by a viral infection, as a result, neutrophil-lymphocyte ratio (NLR) will rise. The

higher NLR, the more severe inflammation will be and it is linked to high mortality and worse prognosis in COVID-19 patients.[10] NLR predicts greater severity in the range of 3.3 to 5.9, while between 7.9 to 11.8 mortality rate will be higher.[11] Four out of five cases in these case series demonstrated lowering of NLR after remdesivir therapy ends, it is associated with better outcomes.

Acute respiratory distress syndrome (ARDS) contributes to a high mortality rate in COVID-19 cases.[12] Severity of ARDS is determined by the partial pressure of oxygen (PaO_2) per fraction of inspired oxygen (FiO_2) also known as PF ratio. Mild ARDS is defined by PF ratio of 300 to 200, 200 to 100 is moderate and less than 100 is severe.13 The five patients in these case series got the first dose of remdesivir after they were admitted to high intensive care unit (HCU) because of ARDS. After five until seven days of remdesivir therapy, three patients recovered from ARDS, one patient had milder severity, and one patient still had moderate ARDS but a higher PF ratio. We associate remdesivir therapy with milder ARDS severity. However, more studies need to be done to prove this.

Remdesivir therapy has some known side effects. A phase one clinical trial demonstrated phlebitis, constipation, headache, ecchymosis, nausea, vomiting and extremities pain after remdesivir was given to healthy subjects. In laboratory examination, the elevation of liver enzymes (SGOT and SGPT), prothrombin, and blood glucose level was founded in less than five percent of subjects.[13] Another study reported diarrhea, skin rash, hypotension, and nephrotoxicity following remdesivir administration.[13] In these case series four patients already had high SGOT and SGPT levels before remdesivir therapy and the level was various after therapy. High initial liver enzyme levels was associated with liver damage caused by SARS-CoV-2 bound with ACE-2 receptor in hepatocyte and hepatic ischemia induced by a cytokine storm.[14]

Renal function tests, such as ureum and creatinine levels should be monitored during remdesivir therapy. Although only a few of remdesivir active forms are excreted in the kidney, they still can be found in urine. To date, there is no specific guideline on remdesivir therapy in mild and moderate renal impairment, but it is not recommended to give remdesivir to the patient with eGFR less than 30 ml/minutes. No study has reported renal impairment in healthy subjects induced by remdesivir therapy, but cautious usage must be done.[13] These case series showed no significant renal impairment in five patients before and after remdesivir was given.

The recommended dosage for remdesivir in COVID-19 was given for 10 days, with an initial bolus dose of 200 mg IV dissolved in 0.9% NaCl or 5% dextrose given for 60 minutes during the first day, for the second day to the tenth day was administered in a dose of 100 mg IV which was diluted and administered for 60

minutes.[15] Patients in this case series received 200 mg of remdesivir on the first day and continued with 100 mg for the following day until the fifth day. For patients with a clinical condition which has not been improved within five days, then remdesivir administration will be continued for up to seven days. Clinical improvement was achieved in four patients after receiving remdesivir therapy for five days, whereas one patient experienced clinical improvement after receiving therapy for seven days. Three to seven days after the last remdesivir administration, these five patients were eventually discharged from the hospital with negative PCR swabs.

In this case series, a good outcome was described, when the patient tested negative on PCR swab after patient with severe symptoms received remdesivir therapy. The administration was following the recommendations of the clinical practice guideline study by Rochwerg et al. published in the British Medical Journal that giving remdesivir intravenously at a dose of 100 mg for 5–10 days is recommended for COVID-19 patients with severe symptoms. We agree with the recommendation while waiting for the results of the large multicenter randomized control trial.[16]

CONCLUSION

The administration of remdesivir in cases of COVID-19 can result in a good outcome, especially its role in reducing the severity and length of treatment. Interaction between remdesivir and other drugs such as heparin, antibiotics, corticosteroid and other therapies need to be considered. Post therapy follow-up needs to be studied further, concerning the assessment of the effectiveness of the therapy. Research on remdesivir is also needed with a larger sample size to prove that it can be used or proven effective in COVID-19.

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Case Report

Pneumocystis Pneumonia in COVID-19 Outbreak: A Case Report - It's not all about COVID-19

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Abstract

One of the phenomena during the current COVID-19 pandemic is Early Detection of In-Patient Deterioration by public health services, especially general hospitals for early detection patients who admit respiratory tract infections (RTIs) symptoms. However, there is a risk of misdiagnosis in differential diagnoses. Pneumocystis Carinii Pneumonia (PCP) is an opportunistic infection that can occur in immunocompromised patients. Symptoms that often appear are similar to COVID-19, such as fever, cough, runny nose, dyspnoea, diarrhea, or others. It makes some difficulties to early diagnosing PCP infection during the COVID-19 pandemic, whereas if it is not early treated it is could be a fatal case. Thus, during the COVID-19 pandemic, it is necessary to consider other differential diagnoses in patients with RTIs symptoms or respiratory distress. It can be supported if other characteristic signs are found during clinical examination, especially if the nasopharyngeal and oropharyngeal swab results are negative.

Keywords: COVID-19, pneumocystis carinii pneumonia, HIV

INTRODUCTION

Cases of Severe Acute Respiratory Syndrome (SARS) Coronavirus 2 infection were first reported in Wuhan, Hubei Province, China in December 2019.[1] These cases of infection had spread to other regions in China. The spread of sporadic cases had led the World Health Organization (WHO) to declare a global pandemic and called this disease "coronavirus disease 2019" (COVID-19).[2]

COVID-19 causes signs and symptoms that vary in each case. The main symptoms that most often appear are fever, dyspnoea, cough, painful swallowing, headache, and runny nose. These symptoms can be exaggerated if there is damage to lung tissue and other organs because the inflammation that occurs can be systemic. This severe condition can result from a widespread inflammatory pathological condition called "cytokine storm".[3]

Cytokine storm is a term that describes the maladaptive process of cytokine release in response to a viral infection or another stimulus.

Dysregulation of the immune response causes tissue damage that can occur in cases of COVID-19 infection.[3]

Pneumocystis Carinii Pneumonia (PCP) or what is now known as Pneumocystis jirovecii is an opportunistic infection in HIV patients. Most PCP cases are seen in HIV cases were not yet known to be or who have not received antiretroviral therapy (ARV).[4]

In PCP cases, lung damage is due to the accumulation of polymorphonuclear neutrophils (PMNs), not by the exposure of infection itself. This will cause surfactant dysfunction which interferes with alveolar development and can result in respiratory failure. The clinical manifestations are usually dyspnoea, cough, or fever. Pneumocystis jirovecii cannot be cultured, so the definitive diagnosis of PCP is by microscopic examination of induced sputum, bronchoalveolar lavage (BAL), or lung tissue.[5]

The PCP case is interesting to be discussed during the COVID-19 outbreak for its similar symptoms. As the COVID-19 pandemic continues to spread throughout the country, hospitals have focused on the early detection of patients who present with symptomatic respiratory tract infections. At the same time, there is a risk of misdiagnosis by another differential diagnosis. Therefore, as clinicians, it is necessary to understand that the signs and symptoms of RTIs are not only about COVID-19.

CASE ILLUSTRATION

A man, aged 50 years old, came with complaints of fever, dyspnoea and dry cough 2 weeks before entering the Emergency Room. Worsening dyspnoea happened by last week. When at home, oxygen saturation can drop to 80% without losing the ability to talk and still be able to do routine. The patient had a weight loss of approximately 3 kg within this month. The patient does not have a history of previous diseases such as heart disease, tuberculosis, hypertension, diabetes, asthma and others. The patient does not have a history of routine drug consumption.

Examination revealed tachypnea, tachycardia and decreased oxygen saturation (SpO_2 80%) and white plaque on the oral mucosa. Oxygen saturation has improved after receiving oxygen therapy. On lung auscultation examination, rough wet rhonchi were found in both lung fields. Chest X-ray shows extensive airspaces consolidation in the right lung and more patchy airspaces opacities in the left lung, possible extensive pneumonia likely due to viral infection.

On non-contrast chest computed tomography (CT) was found extensive ground-glass opacities (GGOs) bilateral and crazy paving appearance. SARS Cov-2 RT-PCR results performed on the same day when the patient arrived and the next 24 hours were negative. Due to the suspicion of immunocompromise, the anti-HIV serum was checked with reactive results.

The working diagnosis for the patient is PCP and HIV. This is based on the symptoms experienced by the patient, including sub-acute fever, cough, and dyspnoea. The immunocompromised sign was demonstrated by the presence of oral candidiasis and significant weight loss. In the CT Thorax supporting examination, there was a crazy paving picture, several times the RT-PCR SARS CoV-2 negative results, HIV laboratory test positive result, and the patient experienced clinical symptoms improvement after receiving treatment. BAL examination could not be done because the patient refused it. In BAL examination, ideally, *P. jirovecii* will be found as the cause of PCP.

The patient received cotrimoxazole therapy for 21 days with a dose equivalent to Trimethoprim 15 mg/Kg, divided into 3-4 doses. The patient also received a corticosteroid, namely Methylprednisolone 62.5 mg intravenously twice a day from the first day the patient was diagnosed with HIV until the patient went home. The patient experienced an improvement in clinical condition and oxygenation, eight days post-treatment. On the 14th day, the patient was discharged and carried out further treatment through outpatient care.

DISCUSSION

During the COVID-19 pandemic around the world, patients who come to health facilities with symptoms of respiratory tract infections (RTI) will be considered to have COVID-19 infection until proven negative. This is to prevent transmission. The initial screening and diagnostic tests are carried out to establish or rule out the diagnosis of COVID-19, such as laboratory, radiology (chest X-ray or non-contrast chest CT) and RT-PCR SARS Cov-2.[6]

COVID-19 can cause a variety of symptoms ranging from no symptoms to severe symptoms and life-threatening. These symptoms can include fever, cough, runny nose, anosmia, ageusia, dyspnoea, nausea, vomiting, diarrhea and other symptoms. The typical symptom that often appears in moderate to severe cases is "Happy Hypoxia". This symptom occurs when a patient with extremely low blood oxygenation, but no sensation of dyspnoea. When the brain receives the signal of internal hypoxia, it gives rise to a sensation of "air hunger", which is curiously absent in severe COVID-19 cases.

The patient showed respiratory symptoms such as fever, dyspnoea and cough which can lead to COVID-19 infection. The phenomenon of happy hypoxia was also shown by the patient. Symptoms were acute, namely 1-2 weeks before hospital admission and had no previous similar symptoms. During the last 2 days, the patient's oxygen saturation was always below 95%.

The results of radiological examinations, both chest X-ray and non-contrast chest CT also pointed to COVID-19 infection was shown through an infiltrate, ground-glass opacity (GGOs) and crazy paving appearance. On this basis, RT-PCR SARS Cov-2 tests have been held twice where the results were

negative/undetectable. This led to the need for other supporting examinations to confirm the differential diagnosis.

The discovery of white plaque on the oral mucosa led to the diagnosis of oral candidiasis, which is common in immunocompromised patients. This was also supported by the symptoms of significant weight loss within the last month. As a comparison, the symptoms of worsening dyspnoea in patients were gradual, but COVID-19 is generally progressive. Therefore, an anti-HIV serum test was performed and the results were reactive.

Symptoms and clinical signs in the patient also result of supporting examination that the diagnosis led to another RTIs (RTI) namely pneumocystis carinii pneumonia. PCP symptoms can appear in varying degrees, ranging from mild and can worsen within days to weeks. However, about 7% of patients are asymptomatic.[4] The physical examination findings in PCP patients are nonspecific, such as tachypnea, tachycardia, use of the auxiliary muscles and rhonchi. The result of CRP (C-Reactive Protein) which increased very high indicates the presence of severe inflammation in the patient's body. Thus, this patient is also given antibiotic therapy.

In addition, the radiological examination can help guide the diagnosis of PCP. The chest X-ray can indeed show a picture of pneumonia (Figure 1). However, this examination is not specific because one in three patients usually shows normal chest X-ray results. Another radiological examination, namely chests CT is a more accurate consideration for detecting PCP because of its high density and sensitivity. On chest CT examination, a ground-glass appearance (crazy paving) will be revealed, which shows the intra-alveolar accumulation of fibrin, debris and organisms (Figure 2 and 3).

In PCP patients without HIV infection, the image of ground-glass opacity will usually be found more often.[6] In this case, the results of the radiological examination such as chest X-ray showed a wide infiltrate, also on chest CT there was a crazy paving image that could match the radiological image on PCP.[5]

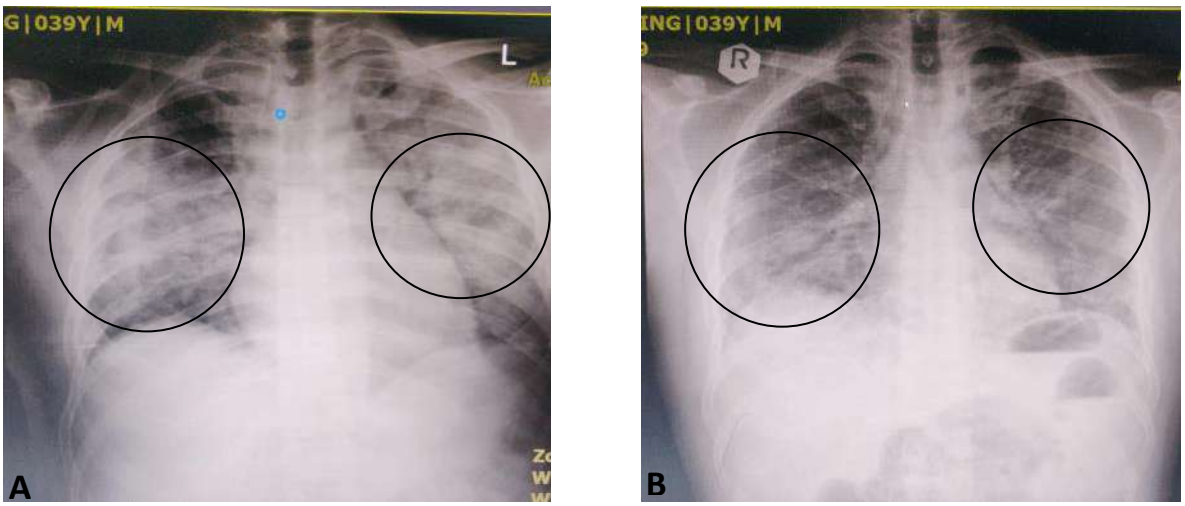

Figure 1. Chest X-ray on A) day 0 of treatment and B) day 14 of treatment

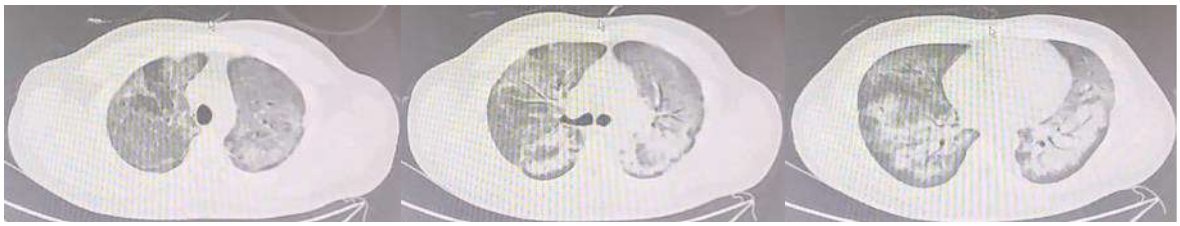

Figure 2. Chest CT scan of the patient's axial cut

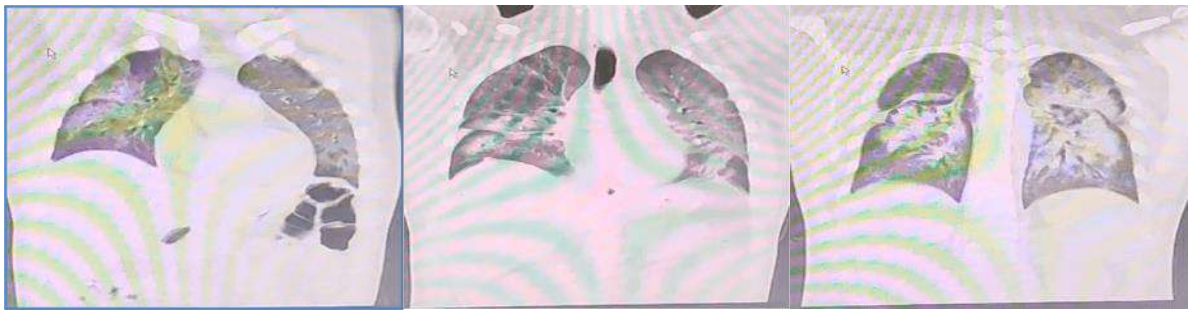

Figure 3. Chest CT scan of the patient's coronal cut

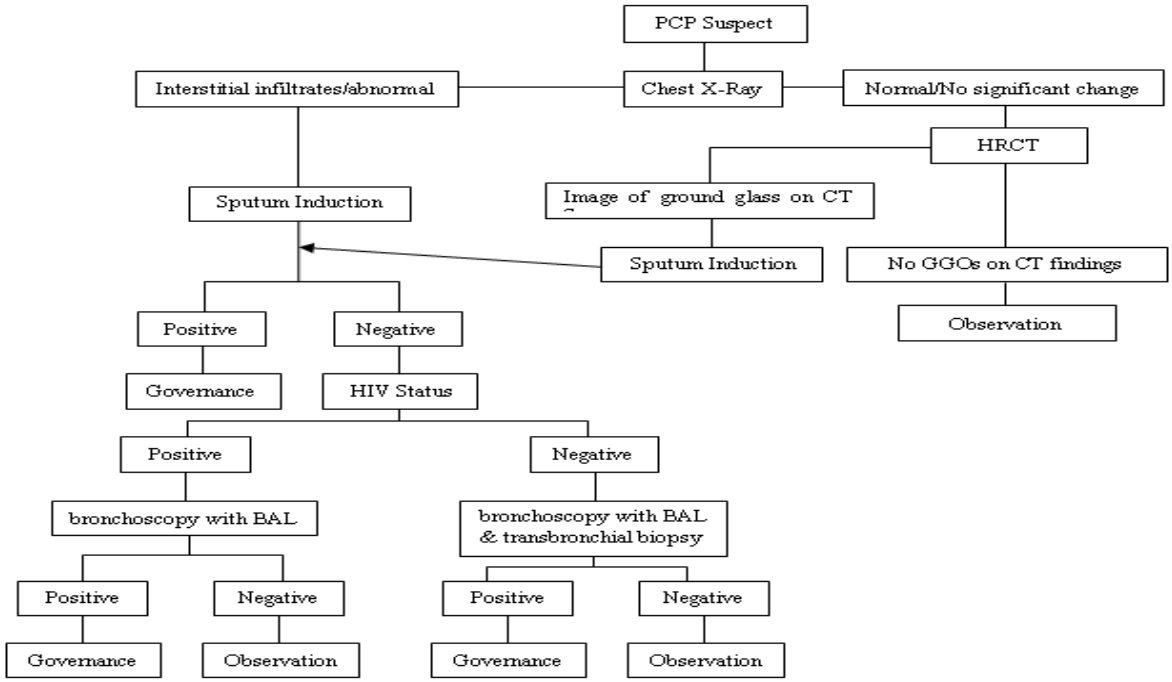

Figure 4. Algorithm of PCP Diagnosis[4]

Table 1. Stratification of disease severity in PCP[5]

	Mild	**Moderate**	**Severe**
Signs and symptoms	Dyspnoea on exertion with or without cough and sweats	Dyspnoea on minimal exertion and occasionally at rest; cough and fever with or without sweats	Dyspnoea and tachypnoea at rest; fever and cough
PaO_2 room air	>83%	61-83%	<60%
SpO_2 room air	>96%	91-96%	<91%
Chest X-ray	Normal or minor perihilar shadowing	Diffuse interstitial shadowing	Extensive interstitial shadowing with or without diffuse alveolar shadowing

The definitive diagnosis of PCP is by finding organisms on the histopathology of sputum that are induced or BAL (Figure 4).[5]

In this patient, sputum induction was performed to examine the PCP organism and also AFB (Acid-fast bacillus). Inevitably, TB infection (Tuberculosis) is also an opportunistic infection in a patient with HIV, but in this one there was no sputum specimen obtained, so no microbiological examination was carried out. Histopathological data from BAL also could not be obtained because the patient refused the procedure with several considerations.

Considering the severe symptoms that lead to PCP and if the therapy is fatal, this patient is still given PCP therapy and other comorbid diseases. Oral or intravenous trimethoprim-sulfamethoxazole (TMP-SMX) for 21 days is the treatment option for PCP with or without HIV. For mild PCP (PaO_2 $\geq$70 mmHg room water), TMP-SMX was administered orally, while moderate-severe degrees (PaO_2 $\leq$70 mmHg room water) were given intravenously. The recommended dosage for PCP therapy is 15-20 mg/kg TMP per day and 75-100 mg/kg SMX per day, divided into 3-4 doses (Table 1).

Patients with a PaO2 <70 mmHg or SpO_2 <92%, need to get prednisone 40mg twice a day on days 1-5, then 40 mg once a day on days 6-10, followed by 20 mg once a day on days 11-21. If the patient can allow for oral therapy then methylprednisolone 75% of the dose is given. The effects of corticosteroids have only been reported when administered 0-72 hours after PCP-specific therapy was started (Table 2).

Table 2.TMP-SMX Desensitization Protocol[7]

Step	Dose
Day 1	80 mg sulfametoxazole + 16 mg trimethoprim (2 ml oral suspension)
Day 2	160 mg sulfametoxazole + 32 mg trimethoprim (4 ml oral suspension)
Day 3	240 mg sulfametoxazole + 48 mg trimethoprim (6 ml oral suspension)
Day 4	320 mg sulfametoxazole + 64 mg trimethoprim (8 ml oral suspension)
Day 5	400 mg sulfametoxazole + 80 mg trimethoprim
Day 6	800 mg sulfametoxazole + 160 mg trimethoprim

The therapeutic response will usually occur on day 7 or so. Especially in PCP patients with HIV, the response to therapy appears longer but not longer than the first eight days. For this patient, cotrimoxazole therapy was equivalent to 20 mg/kg of trimethoprim in 3 divided doses. Treatment response was seen at 7-8 days. The results of chest X-ray evaluation also showed improvement after therapy. This can be seen from the repeat chest X-ray examination on the 14th day of treatment and it was found that the infiltrate intensity was reduced in both lung fields. After the clinical condition improved, the patient could then go for outpatient treatment on day 14.[7]

PCP cases often result in serious infections and a high mortality rate. This makes prevention is very important in risk groups. Trimethoprim-sulfamethoxazole is primary and secondary prophylaxis in addition to dapsone, pentamidine and atovaquone. HIV patients with CD4 <200 cells/µL or with a history of oropharyngeal candidiasis should receive

chemoprophylaxis. Chemoprophylaxis is recommended for life time but can be discontinued in HIV patients if CD4 cell count increases from <200 cells/μL to >200 cells/μL for 3 months, and resumed again if CD4 cell count <200 cells/μL. The dosage given is 1x960mg orally or 1x480mg orally.[7]

According to research, the two doses are equally effective, although side effects are more likely to occur at larger doses. The desensitization process was carried out in patients who were intolerant of TMX-SMX. Desensitization was performed 2 weeks after a mild allergic reaction, which resulted in a temporary interruption of TMX-SMX. Desensitization was not performed for patients with a history of stage 4 hypersensitivity reactions. The following is a desensitization protocol from the World Health Organization (WHO).[7]

CONCLUSION

Since the COVID-19 outbreak occurred throughout the country, hospitals have focused on screening and early detection of patients who come with symptoms of respiratory tract infections leading to COVID-19. Symptoms of respiratory tract infections caused by COVID-19 are indeed similar to symptoms of other respiratory infections. The main symptoms most often present are fever, dyspnoea, cough, painful swallowing, headache, and runny nose. This might cause misdiagnosis with other differential diagnosis risks. Patients presenting with the symptoms listed above, but with negative nasopharyngeal and oropharyngeal swabs, need to be considered of other possible diagnoses. significant weight loss as well as a positive HIV laboratory test result led to an HIV diagnosis.

In patients with or suspected of HIV, if there are complaints of fever, dyspnoea, and/or cough, PCP should be suspected. The clinical picture that appears can vary. PCP symptoms are usually mild and worsen within days to weeks. However, about 7% of patients are asymptomatic. The definitive diagnosis of PCP was confirmed by the BAL test by finding P. Jirovecii. However, in this case, the patient refused to undergo the BAL procedure. The drug therapy for PCP was TMP-SMX for 21 days with a response to therapy generally occurring in the first 7-8 days after starting therapy, as shown in this case. Prophylaxis in PCP-risk groups such as HIV-infected patients is very important as it is associated with significant mortality and morbidity.

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Literature Review

Role of Mesenchymal Stem Cells In Chronic Obstructive Lung Disease

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Abstract

Therapy for Chronic Obstructive Pulmonary Disease (COPD) is currently still not giving effect to tissue repair and regeneration. Chronic Obstructive Pulmonary Disease is still a progressive degenerative disease. Stem cells through their regenerative ability offer a new promising alternative therapy for the management of degenerative diseases including COPD. There have been many studies conducted to determine the safety and efficacy of stem cells in COPD. Published research about stem cells on COPD is still in phase II. Further research is needed on a larger scale before stem cells can be widely applied in the management of COPD. Stem cells are a very promising alternative therapy and are a big leap in the medical world for degenerative diseases including COPD.

Keywords: stem cell, COPD, emphysema

INTRODUCTION

Research on stem cells has rapidly developed in the last 30 years. Stem cells are used by many scientists to study the growth and development process in human tissues and its link with the pathogenesis of the degenerative disease. Stem cells become hope in the medical field as an alternative therapy for diseases unable to be handled by conservative means. Other than its benefits in degenerative diseases, it's not unlikely that in the future stem cells may contribute more in medicine.[1,2]

Research and development of stem cells are often related to issues regarding ethics and religion. Stem cells offer a beneficial economic value if made to be an option of therapy for diseases unable to be treated by conventional therapies, although many controversies also follow. Clinics and health centers offering stem cell application in medicine have been available for the last 20 years. America, Germany, Korea, Thailand and Ukraine have started offering stem cell business to treat many diseases such as diabetes, multiple sclerosis, autism, aging and heart failure.[2]

Data by World Health Organization (WHO) shows that Chronic Obstructive Pulmonary Disease (COPD) is responsible for the fifth cause of global death in 2002 and has risen to be the third in the year 2016. Previously WHO predicted that the

third rank will be reached by 2030. This disease causes about 3 billion deaths worldwide. The figure might increase with longer life expectancy and smoking populations. COPD is marked by lung parenchyma inflammation which causes parenchymal structure damage. Choices of therapy currently available have yet to be able to prevent progressivity and restore tissue damage found in COPD. Stem cell therapy is a big stepping stone in the medical world for degenerative diseases, including COPD.[3]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

One of the non-communicable diseases that becomes an important issue in Indonesia and the world is COPD. The Asia Pacific COPD Round Table Group estimates the number of COPD patients in the Asia Pacific reaches 56.6 million in the year 2006. In Indonesia, there are approximately 4.8 million COPD patients with a prevalence rate of 5.6%. The figure may rise with the escalating number of smokers. Several factors influence the increasing number of COPD patients, such as smoking habits, population growth, longer life expectancy, industrialization and pollution.[3]

Based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019, COPD is a disease marked by airflow limitation which is persistent, progressive, and related to the chronic process of inflammation as a response to gas and dangerous substance exposure. Some risk factors of COPD are cigarette smoke, air pollution, recurrent airway infection, socioeconomic condition, lung growth and development, genetics, and gender. Airflow limitation in COPD is caused by an obstruction in the small airway (bronchiolitis obstruction) and parenchymal damage (emphysema) due to the chronic process of inflammation.[3,4]

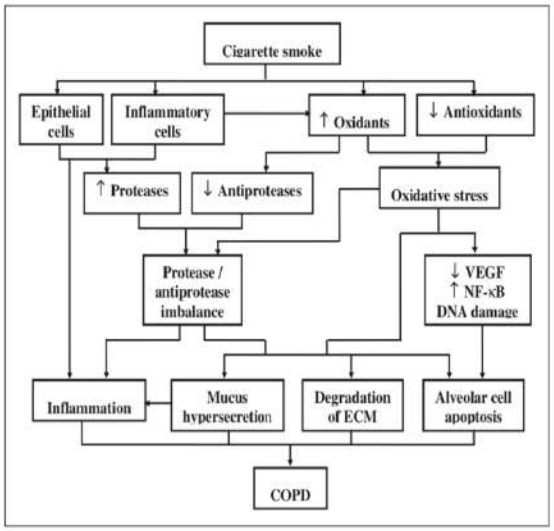

Figure 1. Scheme of COPD pathogenesis[4]

Inflammatory cells involved in COPD are neutrophil, macrophage, T lymphocyte (T4/CD4$^+$ cell and T8/CD8$^+$ cell), B lymphocyte, eosinophil and epithelial cell. The cells release mediators of inflammation such as B4 leukotriene, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor growth factor-β (TGF-β). The process of inflammation causes alveolar damage, airway fibrosis, mucus hypersecretion and release of protease enzyme. Other than inflammation, oxidative stress is also an important mechanism in the development of COPD. Oxidant substances produced by cigarette smoke and pollutants activate an inflammatory gene, inactivates

antiprotease enzyme, stimulates mucus secretion and plasma exudation. The final product of the ongoing process is airflow limitation and air trapping (Figure 1).[3,4]

STEM CELLS

Stem cells are cells that do not differentiate or have not differentiated. Stem cells have the potential to develop into various types of human tissues. Stem cells are the base cells of all multicellular organisms. Stem cells have clonogenic properties or proliferative ability and form an abundant amount of cell colonies from just a single cell. Stem cells have some characteristics such as the ability to reproduce and self-renew, differentiate into various types of functional cell, capability to survive for a long time in proper condition, and the cells activity can be influenced by the external environment.[5,6]

In the last few decades, scientists have researched the biological aspects of stem cells to learn ways to develop them and find a new method to overcome health problems in the medical field. Researchers and doctors hope to discover a new concept of stem cells that may become a huge breakthrough as therapy for current health problems. Several studies are done to find the most effective method to utilize stem cells in treatments. Stem cell-based therapy has been established as a standard of clinical therapy for several diseases such as leukemia, burn injury, corneal damage and abnormality.[5]

The history of stem cell development begun in the middle of year 1800. Scientists found a type of cell able to develop into other cells. The first stem cell was discovered in early 1900 as a cell able to develop into a blood cell. The term stem cell was first coined by a Russian histology expert Alexander Maximov in 1908. Hemopoietic stem cells were first discovered in the fetal umbilical cord in 1978. A scientist from Newcastle University was able to grow artificial liver from an umbilical cord embryonic stem cell in 2006. This show that embryonic stem cell is capable of differentiating into more types of the cell compared to adult stem cell.[5]

Stem cells that have not differentiated can develop into 2 identical cells through the process of mitosis. Those cells can then differentiate into various human tissue. Stem cells can be found in almost every multicellular organism. Stem cells are very important for development, growth and repair of brain, bones, muscle, nerve tissue, blood, skin and other organs of the human body. Stem cells are divided into 5 types based on the potential of differentiation, which are totipotent stem cell, pluripotent stem cell, multipotent stem cell, oligopotent stem cell and unipotent stem cell. Stem cells are also classified based on the source into 2 types, which are embryonic stem cells and adult stem cells.[5]

Totipotent stem cells are a type of stem cell able to differentiate into all kinds of cells. Examples of totipotent stem cells include the zygote from the fertilization of egg cells by the sperm and some cells which were the first result of zygote

division. Pluripotent stem cells can differentiate into almost every type of cell. Examples of pluripotent stem cells are embryonic stem cells and cells from mesodermal, endodermal and ectodermal layers in the early stage of human embryo development. Multipotent stem cell example is hematopoietic stem cell able to differentiate into red blood cell, white blood cell and platelet. The hematopoietic stem cell is a part of the adult stem cell. Oligopotent stem cells can differentiate into some types of cells, such as lymphoid and myeloid stem cells. Other types of stem cell-based on the potential are unipotent stem cells that are only capable of developing into their type. Unipotent stem cells can only develop into similar cells with themselves but can self-repair, therefore replacing damaged tissues.[5,7]

Based on the source, stem cells are divided into embryonic stem cells and adult stem cells. The embryonic stem cell is a stem cell with pluripotent replication ability and able to live for a long duration in proper condition. The embryonic stem cell is found in inner cell mass of blastocyte a few days after zygote development. Different from embryonic stem cells, an adult stem cell has no totipotent properties. Adult stem cells have multipotent properties and are found in certain adult tissues such as umbilical cord or placenta after delivery. The cells can also be found in multiple human tissues after embryonic development. Adult stem cells undergo mitotic multiplication to replace dead cells and repair damaged tissue. The main role of adult stem cell in living organisms is to maintain and repair tissue damage.[5]

In addition to the stem cells mentioned, currently, the third type of stem cell is found, called induced pluripotent stem cell (iPS cells). iPS stem cell is a result of manipulating certain genes that reprogram somatic cells to return to a pluripotent state similar to early human embryonic stage.[5,6]

In the process of stem cell application as therapy for degenerative disease, the stem cell was initially cultured in the laboratory. The culturing process begins by moving cells from the embryo preimplantation phase into a culture plate containing broth. The plate is called culture medium. Stem cells will replicate and spread to the whole surface of the culture medium. Some of the stem cells are moved to a new culture medium after the medium is full. The process is called replating or subculturing. The replating or subculturing process is done repetitively for a few months. The stem cells that have been cultured for 6 months without undergoing proliferation are pluripotent. The cells have normal genetic makeup and are called embryonic stem cells.[5]

The current application of stem cells is to repair damage in tissues unable to repair themselves, therefore body organs can function normally again. Stem cell therapy does not only work by transplanting the stem cells to the body but also prompts the body to keep producing new cells that form healthy tissue. Some applications of stem cells in the medical world include type I diabetes mellitus,

Parkinson's disease, Huntington disease, celiac disease, heart failure, muscle damage and neurological abnormality.[5]

ROLE OF STEM CELLS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Based on the Guideline of Diagnosis and Treatment for COPD by The Indonesian Society of Respirology (ISR) year 2016, strategies of COPD management involve 7 aspects, which are education, smoking cessation, medication, rehabilitation, oxygen therapy, mechanical ventilation and nutrition. Medications for COPD therapy based on GOLD are bronchodilators (anticholinergic, beta-2 agonist and xanthine), anti-inflammation of corticosteroid, antioxidant, mucolytic (ambroxol, edosteine and carbocisteine), antitussive and phosphodiesterase-4 inhibitor (PD4 inhibitor).[3,4]

Those drugs can lessen airflow obstruction, decrease the frequency of exacerbation and improve patient's quality of life, but none can prevent progressivity and reduce the number of deaths. Currently, new perspectives regarding COPD therapy have been revealed through the regenerative property of stem cells. Some studies about stem cells explain the biological effect and mechanism of mesenchymal stem cell (MSC) as a novel approach for COPD therapy.[3,4]

Up until now, stem cell as COPD therapy is still under research. A lot of ongoing study about stem cell as COPD therapy has been done. Three studies that started in 2008 have been completed and published. Daniel J Weiss et al researched 62 COPD patients in 2008 to test the safety and side effects of MSC administration. Research subjects were given intravenous allogeneic MSC with 100 x 10^6 cells/ml dose every month. Every research subject received 4 complete doses for 4 months. The subjects were followed for 2 years. The study found no difference in side effects, frequency of exacerbations and symptoms of worsening on patients that were given MSC compared to placebo. These three studies recruited moderate, severe, or very severe COPD patients.[7,8]

Stessuk, Ribeiro Paes et al did a study in 2009 by administering intravenous stem cells to COPD patients. The study discovered increase of lung function, slowing of tissue degeneration process, improvement of clinical condition enhanced patient's quality of life and no side effects caused.[9,10]

Based on other studies, intravenous MSC administration increase levels of Cluster of Differentiation 31 (CD31) markers. Increased levels of CD31 in the study subjects indicate protective effect and healing response towards tissue damage (Table 1).[11]

Some other researches are still ongoing now. Studies about bone marrow-mesenchymal stem cell (BM-MSC) have yet to be published in Iran, Brazil and Russia. Other than BM-MSC, stem cell originating from the adipose cell is starting to be recognized by researchers.

Table 1. Clinical trial of mesenchymal stem cells in COPD patients.[11]

Clinical trial number	Phase	Treatment	Research subjects	Outcome
NCT 00683722	2	PROCHYMAL™. Bone marrow (BM) MSCs allogenic/placebo $1x10^8$ cells/intravenous administration. Every month for 4 months	62 moderate-severe COPD patients	• Patients were followed for 2 years: There were no toxicity, death and serious side effects. • No significant difference of lung function or indicator of quality of life. • Significant decrease of *C-reactive protein* (CRP) levels 1 month after transplantation.
NCT 01110252	1	Autologous BM MSC; $1x10^8$ IV; single dose	4 severe COPD patients	Patients were followed for 2 years: Improvement of spirometry results, slowing of degeneration process, patient's clinical improvement and increased quality of life.
NCT 01306513	1	Autologous BM MSC. 1-2 celss/kg IV.	7 severe-very severe COPD patients	• No side effect of BM-MSC administration. • Increased level of CD31 marker three times in alveolar septum

Research regarding the safety and efficacy of *adipose-derived stem cell* (ADSC) transplantation in COPD has been done in 7 studies based in the United States of America, Mexico, India and Vietnam. The studies are currently in the process of gathering study subjects.

Comparison of efficacy between BM-MSC and ADSC has also been studied and is currently unfinished. Comparison of both stem cell's efficacy is done by 2 researches in Brazil and the United States of America.[12]

Another study was done by Le Thi Bich et al in Vietnam using umbilical cord-derived mesenchymal stem cells (UC-MSCs) which are intravenously infused with 1.5 x 10^6 UC-MSCs/kg in 20 COPD patients at stages C and D per the Global Initiative for Obstructive Lung Disease (GOLD) classification. Most clinical outcomes remain reduced after 6 months follow up including CRP, Modified Medical Research Council Score, COPD assessment test and number of exacerbations, while the 6MWT score was slightly increased in stage D COPD patients.[13]

A lot of hypotheses has been created regarding stem cell mechanism in the pathogenesis of COPD. Some of those hypotheses have been proven through research towards humans. Other hypotheses are still based on the preclinical stage of trials in experimental animals. Mechanism of repair and stem cell regeneration in COPD includes stem cell suppressing inflammation process, restoring protease-antiprotease enzyme balance, suppressing of the alveolar apoptotic process, suppressing levels of COPD oxidative stress and stem cell having the ability to differentiate as alveolar cells.[4]

MSC Transplantation Suppress Inflammation Process in COPD Pathogenesis

Cigarette smoke and pollutants activate alveolar macrophage in COPD. Activated alveolar macrophage releases pro-inflammatory cytokines such as TNF-α,

IL-1β and IL-6 in the airway and lung parenchyma. Other than pro-inflammatory cytokines, activated macrophage releases chemokines such as IL-8, monocyte chemotactic peptide-1 (MCP-1) and B4 leukotriene that attract neutrophil and T cell. Activated neutrophil proceeds to release oxidants and protease that contributes towards alveolar destruction and mucus hypersecretion in COPD. T cells especially $CD8^+$ after being activated will release cytotoxic perforin, granzyme B and TNF-α that directly contribute to the apoptotic process of alveolar epithelial cells. The final stage of the apoptotic process contributes to emphysematous appearance in COPD.[4]

MSC transplantation in COPD patients induces release of anti-inflammatory molecules and activates the cellular anti-inflammatory pathway. MSC transplantation suppresses the production of pro-inflammatory mediators such as TNF-α, IL-1β, IL-6 and MCP-1. Based on a study by Weiss et al, intravenous allogeneic MSC administration also decreases CRP levels in COPD patients, although there was no difference in exacerbation frequency between the group that received MSC and the control group. A study with a larger scale is needed to learn the effects of MSC in COPD patients more comprehensively.[4]

Hayes et al evaluate inflammation as measured by CRP in 62 moderate to severe COPD patients after given 4 monthly intravenous infusions of either allogeneic MSCs $100x10^6$ cells/infusion or vehicle control. They found that with CRP >4 there was significant reductions in FEV_1 and increases in 6MWT were observed in MSC compared to controls suggest that there is an inflammatory component of the lung disease that may trigger immunomodulatory effects of MSC treatment.[14]

MSC transplantation correlates with the imbalance of protease and antiprotease in the pathogenesis of COPD

The balance between protease and antiprotease enzyme is needed to maintain normal lung structure. The imbalance of protease and antiprotease enzyme (an increase of protease enzyme or decrease of antiprotease enzyme) can induce degradation of the extracellular matrix. The process causes alveolar wall destruction, alveolar epithelial cell apoptosis and mucus hypersecretion.[4]

A study by Mercer et al stated that the process of inflammation and oxidation caused by cigarette smoke increases the production of protease enzyme and suppresses the activity of α-1 antitrypsin enzyme that has antiprotease properties. This phenomenon explains why cigarette smoke becomes the main risk factor of COPD.[4]

Stem cell transplantation can restore the balance of protease and antiprotease enzyme in the lung. A study by Guan et al demonstrated how MSC administration has the opposite effect with matrix metalloproteinase (MMP)-9 dan MMP-12 enzyme activity in messenger ribonucleic acid (mRNA) and protein level. This mechanism has not been fully understood

by scientists. Scientists believed that it is an inhibitory effect by MSC towards protease enzyme produced by inflammatory and epithelial cells which are caused by cigarette smoke and pollutants exposure.[4]

MSC transplantation suppresses alveolar apoptosis in COPD

A balance between the process of apoptosis and cell proliferation is needed to maintain normal lung structure. In COPD there is an imbalance of apoptosis and cell proliferation. An increase of alveolar apoptosis in COPD is not matched by an increase in alveolar proliferation. As a consequence, an emphysematous alveolar structure is formed. The process of apoptosis is influenced by (*Vascular Endothelial Growth Factor*) VEGF. Reduced activity of VEGF seen in COPD patients and smokers is caused by decreased levels of VEGF and VEGF receptor 2 (VEGFR2) in mRNA and protein level.[4]

MSC transplantation in COPD patients can prevent the process of apoptosis by 3 mechanisms. The first mechanism is how MSC stimulates VEGF secretion and induces VEGFR2 receptors. This prevents apoptosis because, in COPD patients, VEGF and VEGFR2 are inhibited. The second mechanism is explained by Zhen et al in their study, that MSC administration in rats stimulates the anti-apoptotic B-cell lymphoma (Bcl)-2 gene and suppresses apoptotic Bax gene. The third mechanism is how MSC transplantation inhibits alveolar *cleaved caspase 3* molecules which are key for cell apoptotic program.[4]

MSC transplantation influences oxidative stress levels in COPD

Oxidative stress contributes to COPD pathogenesis. Two types of oxidants play a role in COPD development, which are oxidants from outside (exogenous) and from inside (endogenous). The most common exogenous antioxidants are cigarette smoke and inhaled pollutants that reach the lungs. Different from exogenous antioxidants, endogenous oxidants are produced by the metabolic reaction of inflammatory cells that were activated by cigarette smoke.[4,13]

In normal conditions, natural antioxidants in the body maintain and protect cells and alveolar tissue from damage by existing oxidants. Cigarette smoke and pollutants cause an imbalance of antioxidants and oxidants in the body that contribute to COPD pathogenesis.[4,13]

MSC transplantation based on a study by Li Ji et al can increase the survival rate of rates with lung damage induced by lipopolysaccharide. MSC transplantation lowers malondialdehyde level which is a marker of oxidative stress. MSC also increases heme oxygenase-1 enzymes in the lung. Heme oxygenase-1 enzyme is a strong antioxidant enzyme and has a protective effect in alveolar cells. Further research is needed to understand more of stem cells' effect on oxidative process in COPD pathogenesis caused by cigarette smoke and pollutants.[4]

The next role of stem cells in COPD pathogenesis is related to their regeneration and differentiation ability. Mesenchymal stem cells transplanted in

emphysematous lungs can differentiate into alveolar cells even though the type of cell is still unclear. A study by Zhao et al demonstrates how MSC administration in rats induces differentiation of type 1 and/or type 2 alveolar cells through signal activation of Wnt (Wingless/Integrated) pathway. The pathway is a molecular pathway with an important role in shaping organs in embryo development. Although the study by Zhao et al was not done in COPD patients, the chance of stem cell's successful role in the disease's therapy gets higher.[4]

CONTROVERSY OF STEM CELLS ROLE AS THERAPY OF OBSTRUCTIVE LUNG DISEASE

Through their regenerative capability, stem cells promise a new alternative to COPD management. A lot of research has been done but it still leaves controversy. Stem cells are also not a part of long-discussed ethical issues. Some aspects of stem cells that became a highlight of ethical aspect are for example the use of stem cells originating from an embryo, gamete cell donor and use of animal oocytes for Somatic Cell Nuclear Transfer (SCNT). Induced Pluripotent Stem Cell is a new type of stem cells that rarely become controversial because it is obtained by induced somatic cells to return to its pluripotent stage.[2]

Studies of stem cell in COPD still has some research limitations that need to be addressed on future research. Some limitations on the current studies are a small number of subjects, the addition of research subject inclusion criteria and the cohort patients were only followed for 2 years. Some studies have been unsuccessful that have weakened the potential efficacy of stem cells in COPD, which is a severe stage of the patients studied may be a major cause of the failure. In addition, to be considered are the sources of MSC and protocol that were used may together have contributed to the results of the studies.

In the coming future, studies with bigger subjects are needed to thoroughly study the efficacy of stem cells and to profile characteristic risk-benefit for COPD patients. A long-term cohort study is also needed to know the side effects and regenerative effects of stem cells.[9,10]The short period of new blood vessel formation after transplantation and survival rate of exogenous MSC in the recipient's body is also a challenge to modify in the procedure of next research.[11,15]

CONCLUSION

Systemic stem cell administration appears to be safe and beneficial from the immunomodulatory effect of MSC treatment. However, the clinical efficacy and understanding of underlying molecular mechanisms remain to be elucidated. Further research is needed on a larger scale before stem cells can be widely applied in the management of COPD. Hopefully, MSC could become an alternative therapy for COPD and other degenerative diseases.

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Editor