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LENGTH OF HOSPITALIZATION AND POLYPHARMACY IN DIABETES MULTIMORBIDITY WITH INFECTIOUS DISEASES

Tasrif Ahmad[1]*, Hari Saktiningsih[1], Firdy Permana[2], Perigrinus Hermin Sebong[3], Yanri Wijayanti Subronto[3], Riris Andono Ahmad[3]
[1]Sekolah Tinggi Ilmu Kesehatan Nasional Surakarta, Jl. Raya Solo - Baki, Bangorwo, Kwarasan, = Grogol, Kabupaten Sukoharjo, Jawa Tengah 57552, Indonesia
[2]PT. Freeport Indonesia, Jl. HR. Rasuna Said Kav. X-7 No.6, Plaza 89, Lt. 5, Kuningan, Karet, Setiabudi, Jakarta Selatan, Jakarta 12940, Indonesia
[3]Center of Tropical Medicine, Universitas Gadjah Mada, Jl. Medika, Sendowo, Sinduadi, Mlati, Kabupaten Sleman, Daerah Istimewa Yogyakarta 55281, Indonesia
*tasrifahmad@stikesnas.ac.id

ABSTRACT
Patients with chronic condition have a higher risk of death and disability than others without chronic condition. Meanwhile, low to middle income countries facing challenges in reducing the burden of Non-Communicable Diseases (NCDs) and controlling infectious diseases such as Human Immunodeficiency Virus, Tuberculosis and Malaria. Patients with Diabetes are more often facing infection than people without diabetes. This research aimed to evaluate the length of hospitalization and polypharmacy in patients with multimorbidity of Diabetes with TB, HIV, and Malaria. Design of this research was a retrospective cohort study. All patients diagnosed with Diabetes since 2008 were grouped according to their illnesses to examine the impact of the diseases from the clinical perspective. Data were collected and extracted from the electronic medical records of PT. Freeport Indonesia since 2008. Determination of level of multimorbidities was performed by using principal component analysis, then the clinical impact of those multimorbidities analyzed using ANOVA tests. Multimorbidities have a significant effect on length of stay (p<0.05) and polypharmacy (p<0.05). The highest need for hospitalization and medication was in the Diabetes-Malaria-Tuberculosis group compared to the other multimorbidity groups. Multimorbidities have a significant impact on length of stay and polypharmacy.

Keywords: diabetes; HIV; malaria; multimorbidities; tuberculosis

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INTRODUCTION

Non-communicable diseases (NCDs) have been predicted to increase every year. The combination of NCDs with other diseases increases the number of multimorbid patients. One of the NCDs that has increased alarmingly is diabetes mellitus (DM). DM was responsible for over 4 million adult deaths in 2017, and more than 75% of people diagnosed with DM live in developing countries (Tripathy, 2018). Indonesia also faces the increasing threat of diabetes similar to the other countries around the world. The International Diabetes Federation in 2017 reported that Indonesia was ranked sixth in the world with about 10.3 million sufferers within the ages of 20-79 years and the DM epidemic is still showing an increasing trend. Diabetes prevalence rate has significantly increased from 6.9% in 2013 to 8.5% in 2018, and as a result, the estimated number of sufferers in Indonesia reached more than 16 million people

who were then at risk of other complications such as: heart attacks, strokes, blindness and kidney failure which can even cause paralysis and death (WHO, 2017).

In addition, low to middle income countries also face challenges in controlling infectious diseases such as Human Immunodeficiency Virus (HIV), Tuberculosis (TB), and Malaria. In Indonesia, TB is still a major burden with the number of cases ranked second worldwide with 10.4 million cases. Along with TB, the number of cases with HIV infections has also increased with new HIV cases continuing to occur including 46,357 new cases in 2017 and as many as 40,468 deaths due to HIV. Meanwhile, the Indonesian government still has serious difficulties to reach the target of Malaria eradication by 2030, since some endemic areas have not yet met the Malaria reduction targets such as Papua, West Papua, East Nusa Tenggara, Maluku and North Maluku (Indonesian Ministry of Health, 2017).

Previous study showed that patients with DM had 2.14 higher risk of infections caused by bacteria, fungi, and viruses than people without diabetes (Casqueiro, Casqueiro & Alves, 2012). DM negatively affects the immune system causing patients to have increased risk of parasitic infection such as Malaria which more commonly occurs in people with Type 2 Diabetes Mellitus (T2DM). One study in Ghana's urban areas found that Plasmodium infection was higher in adult patients with DM (Kalra, Khandelwal, Singla, Aggarwal & Dutta, 2017; Danquah, Bedu-Addo, & Mockenhaupt,2010). Patients with diabetes have a high risk of latent TB transition becoming active TB and also increasing comorbid conditions of the TB disease progression. The development of active TB is more frequent in patients with poor glycemic control. Uncontrolled diabetes can cause multiple complications, one of which is the increased susceptibility to infections through several mechanisms including hyperglycemia and mobile insulinopenia that have indirect effects on the immune function of macrophages and lymphocytes (Silva, et al., 2018). Long-term treatment of HIV contributes to the development of T2DM due to protease inhibition from antiretroviral therapy (ART) drugs which is primarily associated with metabolic disorders (Murphy & Mckay, 2013).

In Papua, A previous study conducted among miners in Mimika reported that there were 1440 cases of T2DM in 2013. Multimorbidity cases with the highest proportion involving malaria reached 5310 cases. The number of NCD cases among the miners reached 3401 cases with T2DM as the most common NCD case (Rodriguez-Fernandez, Ng, Susilo, Prawira, Bangs & Amiya, 2016;). The Mimika Central Bureau of Statistics (2018) reported that Malaria and respiratory tract infections were among the top ten most frequent diseases in Mimika district. In 2016, the number of Malaria cases reported was 5,665 cases. Mimika Regency Health Office (2017) reported that Malaria was the highest ranked among ten major diseases with a total number of 55,680 cases. Meanwhile, in the same time period, the pulmonary TB cases in Mimika were 1,124 cases and HIV/AIDS cases were 184.

Double burden diseases such as HIV-Malaria significantly impact the clinical features. For example, patients with HIV infection have increased risk of Malaria parasitemia, higher Malaria parasite densities, and increased incidence of clinical Malaria, while HIV impairs prophylaxis and treatment of Malaria. Additionally, Malaria contributes to increased HIV replication. There were extreme cases reported in Uganda showing that prevalence of TB-Malaria was low in urban settings, but the study also found triple infection of TB, HIV, and Malaria among rifampicin resistant TB patients (Baluku, et al., 2019). Since the tendency of people with diabetes to suffer from other diseases such as TB, HIV and Malaria will have an impact on clinical outcomes, it is necessary to conduct a study to assess the impact of

multimorbidity between DM and infectious diseases on healthcare services such as length of hospitalization and number of medications (polypharmacy).

METHOD

Design, data source and study setting

The research was an observational analytic study with retrospective cohort design. Research was conducted on PT. Freeport Indonesia (PTFI) workers using secondary data from 2008-2018. PTFI is located in Mimika District, Papua Province, which has been an endemic area of Malaria with a high number of Malaria cases each year. Besides Malaria, Papua also has a high number of TB and HIV cases. All patients with DM diagnosed since 2008 were included in the research, and categorized by their multimorbidity categories. The study included both workers and non-workers of PTFI with T2DM. Using total sampling, data analysis of 1748 patients was conducted based on completetion of the medical record. Sociodemographic factors observed in this study were sex categorized as male and female; job status categorized as PTFI employed and non-employed; ethnicity classified as Papuan and non-Papuan; and age categorized as non-adult (<18 years); young adult (18-35 years old); middle-aged adult (36-55 years old); and older adult (> 55 years old).

Multimorbidity

Multimorbidity were defined by patient morbidity during the ten years of the study period. The multimorbidity groups included: DM, DM-Malaria, DM-Malaria-TB, DM-Malaria-HIV, and DM-Malaria-TB-HIV. Besides grouping by the patients' morbidity, the multimorbidity was also grouped by the level of multimorbidity. Level of multimorbidity was determined by performing principal component analysis (PCA). PCA involved the analysis of factors influencing the level of multimorbidity that will result in the scoring of each type of the disease, meaning the more the prevalence of comorbid disease and episodes of Malaria, the disease score will be higher. After PCA, we then identified levels of multimorbidity in accordance with the existing score. Multimorbidity levels were created from the lowest to the highest levels of multimorbidities. Multimorbidity level was defined as multimorbidity level 1 untill level 4.

Impact of multimorbidity on length of hospitalization and polypharmacy

Length of hospitalization was defined as total days of patient hospitalization in the 10 years of the study, while polypharmacy was defined as total medication prescribed for patients in the 10 years of the study according to electronic medical records. The impact of multimorbidity on length of hospitalization and polypharmacy was analyzed by conducting ANOVA tests. Results with $p<0.05$ were considered statistically significant. This impact was analyzed based on the multimorbidity groups and the level of multimorbidity.

RESULTS

The study included 1748 subjects from a population that consisted of workers and non-workers in PTFI. The samples were mostly aged 36-55 years old and those experiencing multimorbidity were as many as 1054 cases of multimorbidity. Distribution by sex showed most patients were men with 1363 people (77.9%) and those experiencing the most multimorbidity were 984 cases. According to the job category, most subjects in this study were PTFI employees with 1292 people (73.9%), and also those experiencing the most multimorbidity were 961 cases. Distribution of the sample according to ethnicity showed that most subjects were non-Papuan with 1606 people (91.9%) accounting for 1120 cases of multimorbidity (Table 1).

Table 1.
Baseline characteristics and multimorbidity distribution

Sociodemographic factors		N	Multimorbidity						*p value*
			DM	DM-Mal	DM-Mal-TB	DM-Mal-HIV	DM-Mal-TB-HIV	Total Multimorbidity cases	
Age	<18	5	2	3	0	0	0	3	0.000
	18-35	63	22	41	0	0	0	41	
	36-55	1398	344	1,038	8	6	2	1054	
	> 56	282	139	143	0	0	0	143	
Sex	Woman	385	128	257	0	0	0	257	0.079
	Man	1363	379	968	8	6	2	984	
Job	Non-Employees	456	176	280	0	0	0	280	0,000
	Employee	1292	331	945	8	6	2	961	
ethnicity	Non-Papuan	1606	488	1109	6	3	2	1120	0.000
	Papuan	142	19	116	2	3	2	123	

Multimorbidities in this study were divided into several groups: DM (one disease), DM-Malaria (2 diseases), DM-Malaria-TB (3 diseases), DM-Malaria-HIV (3 diseases) and DM-Malaria-TB-HIV (4 diseases). In this study, the highest number of multimorbidities was DM-Malaria group with 1,225 (70.1%) cases, followed by the DM group with 507 (29.0%), and then group DM-Malaria-TB with 8 (0.4%), DM-Malaria-HIV group with 6 (0.3%), and the lowest was in the group of DM-Malaria-TB-HIV with 2 (0.1%) cases. Then, we determined the level of multimorbidity by performing PCA analysis and compared the results with the multimorbidity groups. The results for DM were divided into two levels of multimorbidity with 437 cases in level 1 and the other 70 cases in level 2. Multimorbidity with 2 diseases (DM-Malaria) was divided into 3 levels of the multimorbidities category based on the results of the PCA with 367 cases in level 2, the other 437 cases in level 3, and the rest 421 cases in level 4. This distribution reflected the Malaria episodes experienced by the patients, where the more frequent episodes of Malaria had the higher levels of comorbidity. Meanwhile, patients with HIV and TB were distributed into level 4, which is in accordance with the load in patients with HIV and TB that was high because these diseases require long-term management and treatment programs (Table 2).

Table 2.
Multimorbidity group distribution compared to the level of multimorbidity with PCA analysis

Multimorbidity	Level of Multimorbidity				Total	Percentage (%)
	1	2	3	4		
1 disease (DM)	437	70	0	0	507	29.0
2 diseases (DM-Mal)	0	367	437	421	1225	70.1
3 diseases (DM-Mal-TB)	0	0	0	8	8	0.4
3 diseases (DM-Mal-HIV)	0	0	0	6	6	0.3
4 diseases (DM-Mal-TB-HIV)	0	0	0	2	2	0.1
Total	437	437	437	437	1748	100

DM=Diabetes Mellitus, Mal=Malaria, TB=Tuberculosis, HIV=Human Immunodeficiency Virus

Table 3 shows the results of multimorbidity impact tests on length of stay, and polypharmacy based on the multimorbidity groups. The results show significant impacts on all outcome variables. The greatest impact was in the DM-Malaria-TB group.

Table 3.
Multimorbidity impact on the length of stay and polypharmacy based on the multimorbidity groups

Impact	Multimorbidity	N	Mean	Std. Dev.	*p value*
Length of stay	DM	507	1.00	4.29	0.000
	DM-Mal	1225	3.59	14.06	
	DM-Mal-TB	8	47.37	58.17	
	DM-Mal-HIV	6	28.33	37.88	
	DM-Mal-TB-HIV	2	22	4.24	
Polypharmacy	DM	507	16.31	31.94	0.000
	DM-Mal	1225	27.79	40.32	
	DM-Mal-TB	8	58.25	71.04	
	DM-Mal-HIV	6	41.83	34.33	
	DM-Mal-TB-HIV	2	28	7.07	

DM=Diabetes Mellitus, Mal=Malaria, TB=Tuberculosis, HIV=Human Immunodeficiency Virus.

Table 4.
Impact of multimorbidity on length of hospitalization and polypharmacy based on the level of multimorbidity

Impact	Level of Multimorbidities	N	Mean	Std. Dev.	*p* Value
Length of Hospitalization	1	437	0	0	0.000
	2	437	2.32	6.51	
	3	437	3.63	12.12	
	4	437	6.63	22.06	
Polypharmacy	1	437	11.35	20.36	0.000
	2	437	23.07	39.52	
	3	437	30.59	39.66	
	4	437	33.60	45.48	

Table 4 presents data from the analysis of the impact of multimorbidity based on level of multimorbidity. Multimorbidity had a significant effect on length of stay with p value<0.05. Multimorbidity level 1 had average 0 days length of stay in 10 years, multimorbidity level 2 had an average length of stay of 2.32 days in 10 years, multimorbidity level 3 had an average 3.63 days length of stay in 10 years, and multimorbidity level 4 had an average length with stay of 6.63 days in 10 years. For the impact of multimorbidity on the polypharmacy, there

was a significant impact (p <0.05), where the average number of drugs received by patients in multimorbidity level 4 was 33 drugs in 10 years, multimorbidity group 3 was 30 drugs in 10 years, multimorbidity group 2 was 23 drugs in 10 years, and the multimorbidity group 1 was 11 drugs in 10 years.

DISCUSSION

This research is the first study to assess the impact of multimorbidity on the miners at the PT. Freeport Indonesia, Mimika, Papua, Indonesia. Our study found that multimorbidities of DM with Malaria and TB have the greatest impact, while analyses of data based on the level of multimorbidities found that level 4 category of multimorbidity had the greatest impact on the length of stay and polypharmacy. Diabetes and accompanying diseases are still a serious problem in the world, particularly infectious diseases such as Malaria, TB and HIV. TB and DM have incriminating mutual interactions, mutual complications, making diagnoses and prognoses more difficult and causing worse outcomes (Gennaro, Marotta, & Antunes, 2019). Comorbidity of DM with HIV also has a complex interaction. Comorbid conditions in patients with DM were also identified as a risk factor for severe Malaria in adults who were diagnosed with *P. falciparum* (Wyss, et al., 2017; (Paengsai, et al., 2018)).

Patients with DM have the potential for a longer hospitalization compared with patients without DM, and this finding is in line with other studies' findings showing that the rate of hospitalization for patients with DM was 2-6 times higher than those without diabetes (Comino, et. al., 2015; Sharma, Muir, Johnston, Carter, Bowden & Wilson-Macdonald, 2013). Comorbid DM is associated with prolongation of hospitalization among patients, due to the thrapeutics complexity. One possible explanation for the increased length of stay in patients with DM is the treatment required additional time and more attention to the management of the disease and its complications. Additionally, patients with DM are at higher risk for serious medication errors than non-diabetes patients (Valent, Tonutti & Grimaldi, 2017). Hospitalization rate of TB patients is more likely to be longer in TB patients with comorbidity especially TB-DM (Ronald, et al., 2016). Diabetes together with TB condition makes TB itself more severe and prolonged, and might be mediated by matrix metalloproteinases activities that are considered to be key mediators of TB pathology (Kumar, et al., 2018). Patients with comorbid DM-TB condition have delayed recovery of body mass and dysfunctional hemoglobin, which are important for the functional recovery from the diseases (Faurholt-Jepsen, et al., 2012).

The HIV diabetic population tends to have more chance for development of diabetic complications including diabetic foot disease with possible amputation, and diabetic retinopathy, which causes glaucoma and blindness. Patients with comorbid HIV-DM usually need intensive control of opportunistic infections to reduce these diabetic complications (Wiwanitkit, 2007). The incidence of diabetes in people with HIV increases with the accumulation of ART medications such as stavudine and zidovudine (Saracino, et al., 2012). Malaria-HIV patients, there is a high risk of complications particularly anemia. Severe manifestations of Malaria can occur in people with diabetes even with a lower parasitic count. Relative bradycardia may be due to associated autonomic neuropathy, and may be a marker of subclinical macrovascular complications. Similar vascular pathogenetic mechanisms may explain the higher risk of cerebral, renal, hepatic and cardiac dysfunction in coexistent diabetes and malaria (Kalra, Kalra, Agrawal & Unnikrishnan, 2011; Wyss, et al., 2017). In endemic areas, asymptomatic malaria may be high, and the condition has a significantly negative effect on glycemic control (Udoh, Iwalokun, Etukumana & Amoo, 2019).

The impact on the number of drugs (polypharmacy) also obtained significant results and was directly proportional to multimorbidities. Recent studies on 180,815 adults in primary care reported that approximately 20% of patients with two disease conditions received between 4-9 prescription drugs and 1% received prescriptions for 10 drugs or more. For patients with at least 6 disease conditions, this value increases to 48% and 42%, respectively. Polypharmacy is also associated with drug-induced morbidity such as drug side effects, potential adverse prescribing, and decreased medication adherence. The prevalence of polypharmacy has increased, largely due to changes in population demographics and increased multimorbidity (Wallace, Salisbury, Guthrie, Lewis, Fahey & Smith, 2015). Study in the United States found that there was an increase in the average number of drugs in the 5 therapeutic class with early diagnosis and then increased substantially thereafter to the 7 therapeutic class (Schmittdiel, et al., 2014). The study found a significant result concerning the number of drugs consumed by patients with multimorbidities.

The patients with comorbid DM-TB have worse clinical presentation, with more symptoms, in particular weight loss, fever, dyspnea and night sweats. Additionally, delayed recovery of body mass and dysfunctional hemoglobin have considerable impact on the clinical outcomes of TB. Patients with DM-TB generally in middle-aged adult, have specific family history of DM, hypertension and obesity. However, the clinical significance of these characteristics could be varied. Radiological studies indicate that patients with DM-TB present with more extensive lesions, with greater involvement, with confluent lesions and more frequently cavitary forms. Certain symptoms, such as lethargy, fatigue, weight loss, fever and loss of appetite, are common in both diseases. Consequently, in the presence of such symptoms in patients with DM, the physician may suggest a screening for TB, especially patients DM with uncontrolled glucose level (Pizzol, et al., 2016). There is growing evidence from observational studies that comorbid TB-DM is associated with an increase of adverse TB outcomes, specifically for delays in mycobacterial clearance, treatment failures, death, relapse and reinfection. TB-DM test results are more likely to remain sputum smear positive after completion of the intensive phase of treatment, and this is an early predictor to treatment failure. Patients with TB-DM also appear to have higher risk of relapse with 4-fold risk of relapse versus patients with TB without DM (Restrepo, 2016). Previous research shows that the comorbid DM-TB condition increases relapse, treatment failure and death (Baker, et al., 2011).

These findings showed that it is not only the number of diseases that determine the magnitude of the impact of multimorbidities but also the severity of the disease. Study in India found that the severity was significantly influential in disease multimorbidities (Pati, Swain, Metsemakers, Knottneur & Akker, 2017). In terms of socio-demographics, there are studies which reveal the age-related prevalence of multimorbidity (Puth, Weckbecker, Schmid & Munster, 2017), and indicating women are more likely to experience multimorbidity (Agur, McLean, Hunt, Guthrie & Mercer, 2016). Workers who suffer from chronic diseases over a long period are also at higher risk of remaining ill longer (Sundstrup, Jakobsen, Mortensen & Andersen, 2017). Meanwhile, ethnic variation was associated with multimorbidities in patients with T2DM (Lynch, Gebregziabher, Axon, Hunt, Payne & Egede, 2014).

Active management of the all aspects of comorbidities is the key to improvement of the prognosis in DM patients. Glycemic control should be strictly maintained, particularly, during the initial intensive phase for better outcome in comorbid patients with TB-DM (Siddiqui, Khayyam & Sharma, 2016). There are several management approaches that have meaningful impact on glycemic control: lifestyle modification, moderate-intensive physical activities 3

days per week with minimum 150 minutes in total per week, switching ART regimens from those that had negative impact on glucose control (thymidine analogue, lopinavir/ritonavir). In comorbid patients with DM-HIV, HBA1C is not recommended for glycemic examination because of inaccuracy, instead FPG is recommended. Monitoring examinations should be performed by clinicians every 3 months after starting ART (Monroe, Glesby & Brown, 2015). Patients with DM need to be screened for TB and HIV status, as well as for DM status in patients with TB/HIV. DM should also be considered in the management and prevention of malaria, given the interaction and the significant impact of comorbid conditions (Wyss, et al., 2017; Alebel, et al. 2019; Nascimento & Soares, 2019). Additionally, support laboratory facilities for screening and diagnosis should be further strengthened, including human resources by organizing regular trainings (Majumdar, et al., 2019). Some limitations in this study included using secondary data so that the researchers did not see firsthand the condition of the subjects. Accordingly, further research using primary data and prospective design should be done as a follow-up of the study. The researchers encountered difficult challenges in interpreting the data since there are few studies investigating the combination among the four diseases (DM, HIV, TB, and malaria).

CONCLUSION

Our study found that multimorbidity had a significant impact on length of stay and polypharmacy, both based on the number of diseases experienced by the patients and based on the level of multimorbidity/severity of the diseases. Several management approaches might help to improve patients who experience diabetes with multimorbidity such as lifestyle modification, physical activities, switching regimens and making patient priorities in treatment and monitoring, as well as laboratory diagnosis, including improving human resources skills.

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