

Measurement of Health Related Quality of Life in Malaria Patients in Indonesia using EQ-5D-5L

DIAN AMALIA MAKATITA¹, RESTU NUR HASANAH HARIS², DWI ENDARTI³, CHAIRUN WIEDYANINGSIH⁴, TRI MURTI ANDAYANI⁵

ABSTRACT

Introduction: Indonesia is one of the countries with high malaria cases. In 2017 there were at least 261,167 malaria cases nationally. West Papua is included in the 3 major provinces with the highest incidence of malaria. Malaria disease alters patient's Quality of Life (QoL). Thus, measurement of Health Related Quality of Life (HRQOL) is gaining importance.

Aim: This study was aimed at measuring HRQOL in malaria patients and examining the relationship between socio-demographics and HRQOL.

Materials and Methods: Data were collected from 110 patients with malaria visiting primary healthcare centres. It was a cross-sectional study conducted from October to December 2018. Measurement of HRQOL was done using the European Quality of Life-Five Dimension-Five Level (EQ-5D-5L) instrument. Descriptive analysis was used to analyse patients HRQOL in terms of EQ-5D-5L descriptive system, EQ-5D-5L index scores

(utility), and European Quality-Visual Analog Scale (EQ-VAS). Relationships between socio-demographics and HRQOL were examined using multivariate regression analyses.

Results: Almost all of the respondents reported problems in all domains. There were no responses of "extreme problems" for any of the domains. "Pain/discomfort" (99%) and "usual activities" (95.4%) domains were the most reported problems among malaria patients. The mean EQ-5D-5L and VAS score was 0.490 ± 0.470 and 50.9 ± 0.5 , respectively. Utility score in patients with severe malaria (0.349) was lower compared to patients with mild malaria (0.571). Patients with health insurance had a better QoL. Sociodemographic factors, particularly the type (severity) of malaria and health insurance, contributed 36.9% to the HRQOL.

Conclusion: Malaria was associated with poor HRQOL and particularly affected "Pain/discomfort" and "usual activities" domains.

Keywords: Health utility, Pharmacoeconomics, Tropical disease

INTRODUCTION

According to the World Malaria Report 2018, there were 219 million cases of malaria globally in 2017 (uncertainty range 203-262 million) and 435,000 malaria deaths [1]. In Indonesia itself, there were 261,617 cases of malaria in 2017, which killed at least 100 people. West Papua, which is included in the 3 major provinces with the highest malaria incidence, reported 9,110 malaria cases in 2016 [2].

The concept of QoL is very useful for the process of improving health, holistic therapy and care, and for the rehabilitation process [3]. Researches on QoL must take into account the patients' somatic conditions, mental status, social relations and physical fitness. Health condition is one of the basic factors affecting QoL [4]. Malaria affects work productivity, with negative consequences for economic growth, which limits living conditions, supports the spread of disease in the population, which in turn will suffer a vicious circle of disease and poverty [5].

HRQOL could be measured using generic or specific instrument based on the purpose of measurement. The generic instrument is classified into health profiles and preference-based measures approach. Meanwhile, specific instrument measures the health profiles based on disease-specific, population-specific, function-specific, and condition- or problem-specific [6]. Example of specific instruments are Diabetes Quality of Life Clinical Trial Questionnaire-Revised (DQLCTQ-R) and Diabetes Specific Quality of Life Scale (DSQOLS) for measuring HRQOL of diabetes mellitus patients [7], the Dartmouth Cooperative Functional Assessment Charts (COOP) for measuring HRQOL in paediatrics [8], and Functional Outcomes of Sleep Questionnaire (FOSQ) for measuring HRQOL in obstructive sleep apnea [9]. Among the generic instruments to measure health profiles, Short Form (SF-36) is the most commonly used. The Quality of Well-Being (QWB) Scale, the Health Utilities Index (HUI), and

the EuroQol Instrument (EQ-5D) are preference-based measures designed to summarise HRQOL in a single number ranging from 0 to 1, namely health utility (utility) [10]. Utility is necessary in economic evaluation/pharmacoeconomic studies to calculate quality of adjusted life years (QALY), which is an outcome used in cost utility analysis, one of method in pharmacoeconomic study. The concept of Quality Adjusted Life Years (QALYs) is a multiplication of HRQOL in term of utility and duration of life [11].

The aim of this study was to measure HRQOL on malaria patients using EQ-5D-5L instrument and examine the relationship between socio-demographic and HRQOL.

MATERIALS AND METHODS

Study Design and Participants

This was a cross-sectional study, conducted from October to December 2018 (3 months) involving malaria patients who visited primary healthcare centres in Manokwari District, West Papua Province, Indonesia.

The inclusion criteria were a positive malaria diagnoses, age 18 years or above, and an ability to communicate well. The exclusion criteria were those who had serious diseases that might interfere QoL such as diabetes mellitus, chronic kidney disease, and cardiovascular disease; as well as pregnant mother. Sample size was determined using the following formula [6]:

$$n = \frac{\sigma^2}{(\omega/1.96)^2}$$

n=sample size required (number of responders to survey)

σ =the standard deviation of utility mean from previous study

ω =precision or margin of error

1,96=the standard normal variate at 5% type 1 error ($p < 0.05$)

The previous study of QoL measurement of malaria patients with 11 and 20 responders resulted Standard of Error (SE) of utility 0.003-0.061, hence the standard deviation were 0.13-0.26 [12]. Using the 0.05 (5%) precision, the sample size was calculated as 26-103 responders. In this study we recruited 110 malaria patients as study sample.

Study Site

Data were collected from four primary healthcare centres in three different areas of Manokwari Districts, which were Maripi from the South, Sanggeng and Amban from the West and Pasir Putih from the East. Study sites were selected based on the considerations of high prevalences of malaria in those healthcare centres and the accessibility of locations.

Research Instrument and Data Collection

The EQ-5D-5L instrument in Bahasa Indonesia language version, developed by EuroQoL group was applied in this study [13]. The instrument consists of two parts. The first, namely EQ-5D-5L descriptive system, consists of five dimensions: "mobility", "self-care", "usual Activity", "pain/discomfort" and "anxiety/depression". Each domain has five levels of possible response. For instance, mobility asking about walking, the response is either no problems (level 1), or slight problem (level 2), or moderate problem (level 3), or severe problems (level 4), or unable to walk/extreme problems (level 5). Responses for the 5 domains is called the health state. For example, the health state "12345" indicates that there is no problem (level 1) in the dimension of mobility, having slight problems in the dimension of usual activity, having moderate problems (level 3) in the domain of self-care, having severe problems (level 4) in the dimension of pain/discomfort, and having extreme problems (level 5) in the dimension of anxiety/depression. The second part is the European Quality-Visual Analog Scale (EQ-VAS), consisting of the value of 0-100 units of the 'thermometer type' scale, where the value of 0 means died and 100 means perfect health [14].

Utility or EQ-5D index score was converted from EQ-5D-5L descriptive system using value set of Indonesia which represents Indonesian population [15].

Meanwhile VAS score was calculated using the following formula: the number respondent select on the 'thermometer type' scale, divided by 100.

An additional questionnaire consisted of patient sociodemographics, namely, age, gender, marital status, Education attainment, monthly income, occupation, type of malaria, family history, health problems, and health insurance. The patients were interviewed face-to-face by researchers using EQ-5D-5L and prepared questionnaire after signing an informed consent.

STATISTICAL ANALYSIS

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 21). Descriptive analysis included mean, standard deviations and frequencies, which were used to analyse socio-demographics of patients, EQ-5D-5L descriptive system, EQ-5D-5L index scores (utility), and EQ-VAS. Normality test of the data was tested using Kolmogorov-Smirnov test. Independent t-test was used to compare differences between mean of utility score among malaria patients. Chi-square test was performed to analyse cross tabulation between patient socio-demographics and EQ-5D descriptive system. Correlation between socio-demographics and utility score used Spearman's ranks correlation. Influence of socio-demographic on HRQOL were explored using multivariate regression analyses.

Ethical Considerations

This study obtained the ethical approval from Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine

Gadjah Mada University-Dr Sardjito General Hospital with the reference number of Ref: KE/FK/0472/EC/2018. The study began after receiving permissions from each study site of primary healthcare centres. Informed consents were collected from all study participants.

RESULTS

Patients Socio-Demographics

Patient demographic characteristics are shown in [Table/Fig-1]. Out of 150 malaria patients recruited, 110 malaria patients met the inclusion criteria and were included in the study. The mean age of the patients was 33±12.7 years. The highest number of patients was in the age group 18-30 years (57.3%). Most of the respondent's education level was below high school (63.6%). Approximately 49.1% of the respondents were employed. Most respondents were married (63.6%). Most of the respondents had a monthly family income above Rp. 3,000,000 (56.4%). [Table/Fig-1].

Demographic characteristics	Number of patients (%) (N=110)
Gender	
Male	47 (42.7)
Female	63 (57.3)
Age (years)	
17-30	63 (57.3)
31-50	36 (32.7)
>50	11 (10)
Mean±SD	33.39±12.794
Educational attainment	
<High school	70 (63.6)
>High school	40 (36.4)
Employment status	
Employed	54 (49.1)
Unemployed	56 (50.9)
Income	
<Rp. 3,000,000	48 (43.6)
> Rp.3,000,000	62 (56.4)
Marital status	
Married	70 (63.6)
Single	40 (36.4)
Type of malaria	
Severe	40 (36.4)
Mild	70 (63.6)
Family history of any disease	
Yes	31 (28.2)
No	79 (71.8)
Other health problems	
Yes	45 (40.9)
No	65 (59.1)
Health insurance	
Yes	103 (93.6)
No	7 (6.4)

[Table/Fig-1]: Demographic characteristics malaria patients (2018, N=110).

The types of malaria in the area of Manokwari Regency included mild malaria (63.6%) and severe malaria (36.4%). Severe malaria is defined as acute falciparum malaria (malaria tropica) with signs of severity and/or evidence of vital organ dysfunction. Mild malaria is of less severity and caused by *Plasmodium ovale* and *Plasmodium vivax* (Malaria tertiana), *Plasmodium malariae* (Malaria quartana) and *Plasmodium knowlesi* [16].

EQ-5D Descriptive System

Patients' responses to five dimensions of EQ-5D-5L descriptive system were called health states. In this study we found 33 types of health states, with the highest health state being 22222, with 14 respondents (12.73%), followed by health state 33333, with 12 respondents (10.9%). The utility value for health state 22222 was 0.525 and for health state 33333 was 0.307 [Table/Fig-2].

Health state	Health utility	Number of patients	Percentage (%)
11121	0.914	4	3.6
11122	0.835	1	0.9
11221	0.824	5	4.5
12221	0.723	4	3.6
21221	0.705	9	8.2
21222	0.626	3	2.7
21223	0.571	1	0.9
21333	0.496	1	0.9
22211	0.690	1	0.9
22221	0.604	3	2.7
22222	0.525	14	12.7
22223	0.470	9	8.2
22232	0.516	6	5.5
22233	0.461	5	4.5
22323	0.404	1	0.9
22332	0.450	2	1.8
22333	0.395	3	2.7
23332	0.411	1	0.9
23333	0.356	1	0.9
32221	0.531	1	0.9
32322	0.386	2	1.8
32323	0.331	1	0.9
32331	0.456	1	0.9
32332	0.363	4	3.6
32333	0.322	2	1.8
32342	0.358	2	1.8
32433	0.138	1	0.9
33332	.0338	3	2.7
33333	0.307	12	10.9
33342	0.235	2	1.8
33343	0.180	3	2.7
33443	0.035	1	0.9
44444	-0.384	1	0.9

[Table/Fig-2]: Health state of HRQOL malaria patients measured with EQ-5D-5L. HRQOL: Health related quality of life; EQ-5D: European quality of life five-dimension. digits represent response level (1-5) for five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)

[Table/Fig-3] presents responses for each domain of EQ-5D-5L descriptive system. Almost all of the respondents reported having problems in any of the domains. There were no responses for "extreme problems" for any of the domains. "Pain/discomfort" and "usual activities" domains were the most reported problems in malaria patients. Number of patients who reported having problems was 87.3% for "mobility", 78.2% for "self-care", 95.45% for "usual activities", 99.1% for Pain/Discomfort, and 74.5% for "anxiety/depression".

From the results of the Chi-square test [Table/Fig-4], it can be seen that age significantly influenced patients' reporting problems associated with QoL, particularly in the domains of "self-care" ($p=0.039$) and "anxiety/depression" ($p=0.014$). Frequency of "some problems" was significantly higher for mild malaria patients in the domains of "mobility" ($p=0.002$), "self care" ($p=0.000$), and "anxiety/

depression" ($p=0.000$). It was found that patients with severe malaria did not have many problems in other dimensions. The frequency of respondents having problems was higher in the married group ($p=0.002$).

Dimension	N	%	Response of having problems (%)
Mobility			
No problems	14	12.7	87.27
Slight	61	55.5	
Moderate	34	30.9	
Severe	1	0.9	
Unable/Extreme	0	0	
Self-care			
No problems	24	21.8	78.18
Slight	62	56.4	
Moderate	23	20.9	
Severe	1	0.9	
Unable/Extreme	0	0	
Usual activities			
No problems	5	4.5	95.45
Slight	63	57.3	
Moderate	39	35.5	
Severe	3	2.7	
Unable/Extreme	0	0	
Pain/Discomfort			
No problems	1	0.9	99.09
Slight	59	53.6	
Moderate	42	38.2	
Severe	8	7.3	
Unable/Extreme	0	0	
Anxiety/Depression			
No problems	28	25.5	74.54
Slight	41	37.3	
Moderate	40	36.4	
Severe	1	0.9	
Unable/Extreme	0	0	

[Table/Fig-3]: Response of some problems malaria patients with EQ-5D.

EQ-5D Score and VAS Score

The EQ-5D score and VAS score based on socio-demographic groups are presented in [Table/Fig-5]. The mean EQ-5D-5L score patients was 0.49 ± 0.20 , while the mean VAS score was 0.509 ± 0.117 . The EQ-5D-5L score was slightly lesser than the VAS score. In this study, the mean EQ-5D score (0.349 ± 0.126) and VAS score (0.434 ± 0.088) in patients with severe malaria was significantly lower ($p=0.000$ and $p=0.000$ for EQ-5D score and EQ-VAS, respectively) compared to patients with mild malaria in which the mean EQ-5D score and EQ-VAS were 0.571 ± 0.195 and 0.553 ± 0.11 , respectively.

There was also significantly higher ($p=0.044$) mean EQ-5D score in patients having health insurance (0.500 ± 0.191), compared to those not having health insurance (0.341 ± 0.321). Nevertheless, there was no significant difference in the VAS score.

Results of multivariate regression analysis showed that two variables of the socio-demographics criteria, namely, type of malaria and health insurance, were found to be correlated with EQ-5D index score of malaria patients ($p=0.05$). These variables contributed to 36.9% of EQ-5D index score of malaria patients ($R^2=0.369$) [Table/Fig-5,6].

	MO		SC		UA		PD		AD	
	% of having problems	p-value	% of having problems	p-value	% of having problems	p-value	% of having problems	p-value	% of having problems	p-value
Gender										
Female	36.3	0.556	34.5	0.558	40.9	0.637	41.8	0.427	29.0	0.179
Male	50.9		43.6		54.5		57.2		45.4	
Age										
17-30	47.2	0.051	40	0.039*	53.6	0.124	56.3	0.571	37.2	0.014*
31-50	31.8		30		32.7		32.7		30	
>50	8.18		8.1		9.09		10		7.2	
Education attainment										
< High school	55.4	0.957	49	0.727	60.9	0.601	62.7	0.636	48.1	0.710
> High school	31.8		29		34.5		36.3		26.3	
Employment status										
Employed	43.6	0.617	41.8	0.081	48.1	0.364	49	0.509	37.2	0.744
Unemployed	43.6		36.3		47.2		50		37.2	
Income										
<Rp. 3,000,000	37.2	0.607	32.7	0.477	40.9	0.651	43.6	0.564	35.4	0.156
> Rp.3,000,000	50		45.4		54.5		55.4		39.0	
Marital status										
Married	57.2	0.256	52.7	0.116	61.8	0.351	63.6	0.364	53.6	0.002*
Single	30		25.4		33.6		35.4		20.9	
Type of malaria										
Severe	36.3	0.002*	35.4	0.000*	36.3	0.157	36.3	0.636	34.5	0.000*
Mild	56		42.7		59.0		62.7		40	
Family history										
Yes	25.4	0.753	24.5	0.156	27.2	0.565	28.1	0.718	24.5	0.058
No	61.8		53.6		68.1		70.9		50	
Health problems										
Yes	35.4	0.874	32.7	0.701	38.1	0.398	40.9	0.591	33.6	0.124
No	51.8		45.4		57.2		58.1		40.9	
Health insurance										
Yes	80.9	0.592	71.8	0.343	89.0	0.715	92.7	0.936	68.1	0.188
No	6.3		6.3		6.3		6.36		6.3	

[Table/Fig-4]: Patient response to problems in EQ-5D-5L (N=110).

EQ-5D-5L: European quality of life- 5 dimension- 5 level; MO: Mobility; SC: Self care; UA: Usual activity; PD: Pain/discomfort; AD: Anxiety/depression. p<0.05

p-value: chi-square test; No marks: not significant

DISCUSSION

To the best of our knowledge, this is the first study to measure HRQOL among malaria patients in Indonesia, particularly using EQ-5D-5L. We measured health status with EQ-5D descriptive system and converted to EQ-5D score using the value set for the Indonesian population.

In this study, all of respondents reported problems in any domain and, none of them reported full health state of 11111. Furthermore, the most reported domains of having problem were "pain/discomfort" (99%) and "usual activities" (95.4%). This indicated that malaria affected patient QoL due to "pain/discomfort" and since the patients were incapable of conducting "usual activities". Other diseases might also affect patients' QoL through different domains. For example, the most reported problems in dengue fever were "self-care" (71.8%) and "usual activities" (64.6%) [17]. The most reported problems in cervical cancer were "pain/discomfort" (67.8%) followed by "anxiety/depression" (57.5%) [18]. The most reported problems in type 2 diabetes mellitus were "pain/discomfort" (76.33%) and "usual activities" (48%) [19]. The most reported problems in Indonesian general population were "pain/discomfort" (39.7%) and "anxiety/depression" (34.3%) [20].

McCarthy AE et al., reported that the HRQOL in terms of VAS score among malaria patients was 0.539(SE=0.039) [12], which was

comparable to the VAS score among patients with simple malaria in Indonesia, that exhibited a VAS score of 0.509±0.117. The results of this study showed that utility (EQ-5D index score) among malaria patients in Indonesia (0.49±0.20) was lower than other similar tropical diseases in other settings. For instance, the mean EQ-5D index score of Dengue Fever (DF) patients was 0.66 [17] and that of tuberculosis patients was 0.69 [21]. A study to measure QoL among malaria patients in Nigeria revealed that the majority of patients did not accept that they were suffering from malaria, which might have led to lower QoL [22].

The utility score among malaria patients was lower when compared to the utility of other diseases in Indonesia measured using the same instrument of EQ-5D, for instances the value of cervical cancer was 0.76±0.2 [17], while that of other, human papillomavirus (HPV) related cancers was 0.69±0.10 [23], and type 2 diabetes mellitus was 0.74±0.22 [19]. The utility of general population of Indonesia was 0.91 [20]. This indicates that the utility decrement of malaria patients from general population was about 0.42.

In this study, socio-demographic variables that significantly influenced QoL were age, marital status, and type of malaria severity. This finding was inline with a study conducted by Van Damme Ostapowicz K et al., [22] which indicates that age affects the social domain, especially in those over 50 years of age. Findings

	EQ-5D score			VAS score		
	Mean	(SD)	p-value	Mean	(SD)	p-value
Total	0.490	0.203		0.509	0.117	
Gender			0.734			
Female	0.482	0.207		0.499	0.123	0.430
Male	0.496	0.202		0.517	0.113	
Age			0.161			
17-30	0.516	0.227		0.514	0.117	0.171
31-50	0.437	0.145		0.486	0.108	
>50	0.516	0.205		0.56	0.133	
Education attainment			0.689			
< High school	0.496	0.202		0.514	0.122	0.539
> High school	0.480	0.208		0.50	0.109	
Employment status			0.220			
Employment	0.466	0.189		0.50	0.113	0.418
Unemployment	0.513	0.215		0.518	0.121	
Income			0.979			
<Rp. 3,000,000	0.489	0.224		0.504	0.130	0.681
> Rp.3,000,000	0.490	0.188		0.513	0.106	
Marital status			0.559			
Married	0.481	0.166		0.512	0.107	0.718
Single	0.505	0.257		0.504	0.134	
Type of malaria			0.000*			
Severe	0.349	0.126		0.434	0.088	0.000*
Mild	0.571	0.195		0.553	0.110	
Family history of any disease			0.607			
Yes	0.474	0.158		0.517	0.117	0.665
No	0.496	0.219		0.506	0.117	
Health problems			0.674			
Yes	0.500	0.176		0.528	0.104	0.158
No	0.483	0.221		0.496	0.124	
Health insurance			0.044*			
Yes	0.500	0.191		0.510	0.114	0.698
No	0.341	0.321		0.492	0.161	

[Table/Fig-5]: HRQOL malaria patient with EQ-5D and VAS score. (N=110). HRQOL: Health related quality of life; EQ-5D: European quality of life- 5 dimension; VAS: Visual analog scale; SD: Standard deviation. p<0.05. Notes: independent t- test; No marks: not significant.

Variable	R	SE	Beta	t	p-value
Type malaria	-0.627	0.033	-0.588	-7.504	0.000*
Health insurance	0.108	0.065	0.308	3.932	0.000*
Constant score		0.62		5.527	0.000*

R=0.607 R²=0.369 R²Adj=0.357 F=31.283 p-value=0.000*

[Table/Fig-6]: Analysis with multivariate regression.

SE: Standard error; t: t-test; p-value: Significant for variable; R: Multicorrelation coefficient; R²: Multiple regression correlation coefficient; R²Adj: Adjusted R value. *p<0.05

of the study conducted by McCarthy AE et al., showed that prevalence of severe malaria affects the time of hospitalisation when compared with mild malaria, which worsens patients' QoL [12]. A study of conducted by Sakamaki H et al., in type 2 diabetes mellitus patients showed that the frequency of having problems was higher in patients with complications (more severe) than in those without complications (less severe) [24].

LIMITATION

This study is limited by the small sample size, which therefore, does not represent the whole of Indonesia, but only the Manokwari region. However, this study provides insight regarding HRQOL in malaria patients in a particular part of Indonesia.

CONCLUSION

This study focuses on measuring the QoL in malaria patients in Manokwari, Indonesia. Malaria was associated with poor HRQOL and particularly affected "Pain/discomfort" and "usual activities" domains. The type (severity) of malaria and health insurance were found to be correlated with QoL on malaria patients. These findings suggest that, measurement of QoL in malaria patients using EQ-5D-5L provides an overview of their own health status and it also helps health workers to provide care to patients and focus on some problem domains.

Fundings: This research was supported by the Ministry of Research, Technology and Higher Education Republic of Indonesia.

ACKNOWLEDGEMENTS

This study is part of a research thesis of Dian Amalia Makatita while studying Master Program in Faculty of Pharmacy, Universitas Gadjah Mada.

Authors contribution: Concepts and ideas: DE. Design: DE, CW, TMA. Definition of intellectual content: DE. Literature search: DE, DAM, RNH. Data acquisition: DAM. Data analysis: DAM, RNH. Statistical analysis: DE, DAM, RNH. Manuscript preparation: DE, DAM, RNH. Manuscript editing: DE, DAM, RNH. Manuscript review: DE, DAM, RNH, CW, TMA.

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PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Master in Pharmacy Management, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
2. Research Assistant, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
3. Lecturer, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
4. Lecturer, Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
5. Lecturer, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Dwi Endarti,
Sekip Utara Rd, Yogyakarta, Indonesia.
E-mail: endarti_apt@ugm.ac.id

Date of Submission: **Apr 19, 2019**
Date of Peer Review: **May 06, 2019**
Date of Acceptance: **Jun 04, 2019**
Date of Publishing: **Jul 01, 2019**

FINANCIAL OR OTHER COMPETING INTERESTS: None.