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ARTIKEL JURNAL INTERNASIONAL SCOPUS Q4

Judul artikel: The prevalence of Diabetes Mellitus among Tuberculosis Positive Case in Surabaya
Jurnal : Malaysian Journal of Medicine and Health Science, 16 (1)
Author : Putri, E.I.S; Indriati, D.W & Wahyunitisari M.R.

No	Perihal	Tanggal
1	Bukti pengiriman artikel	12 November 2018
2	Bukti hasil review I	27 Juni 2019
3	Bukti pengiriman revisi I	09 Juli 2019
4	Bukti hasil review II	31 Juli 2019
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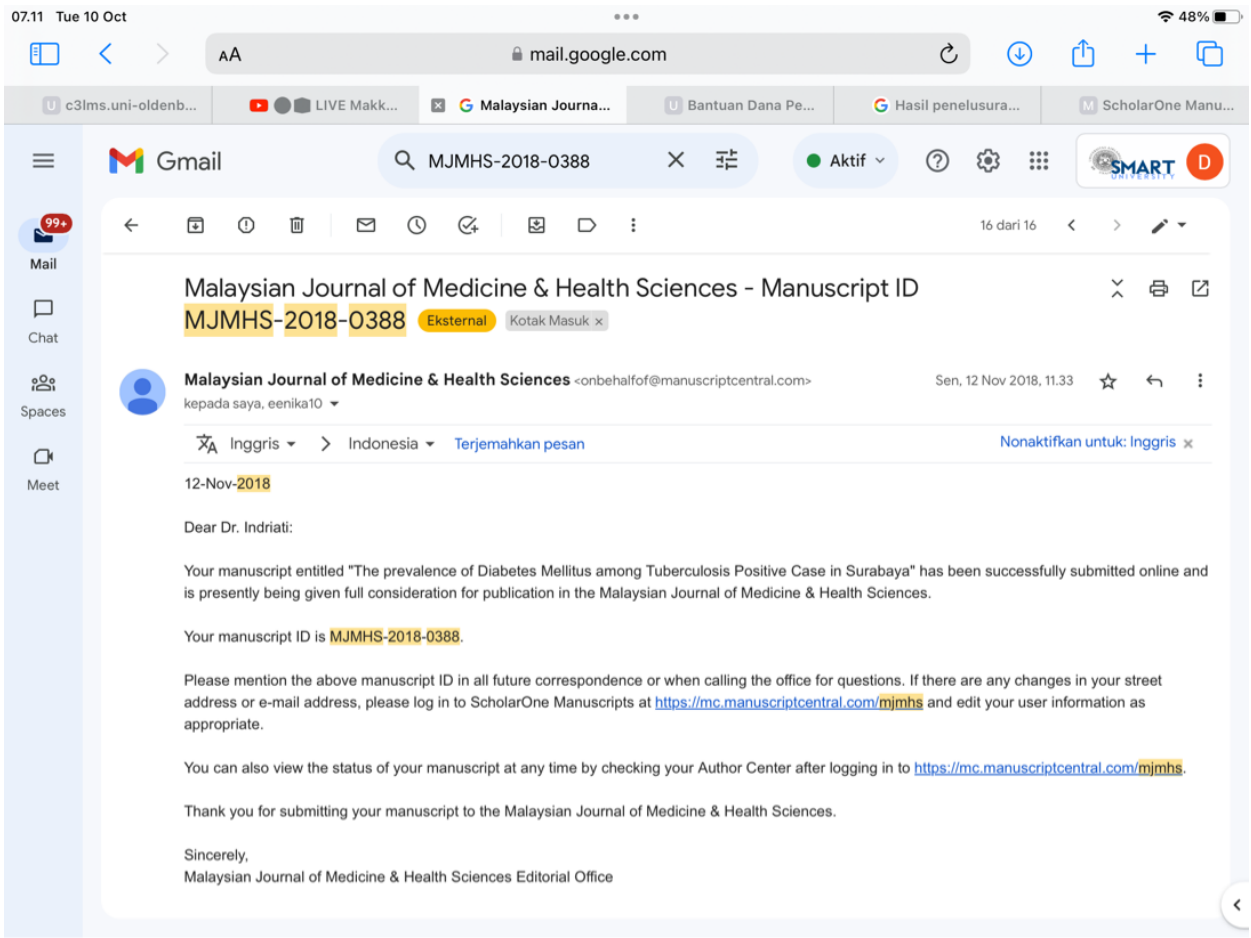
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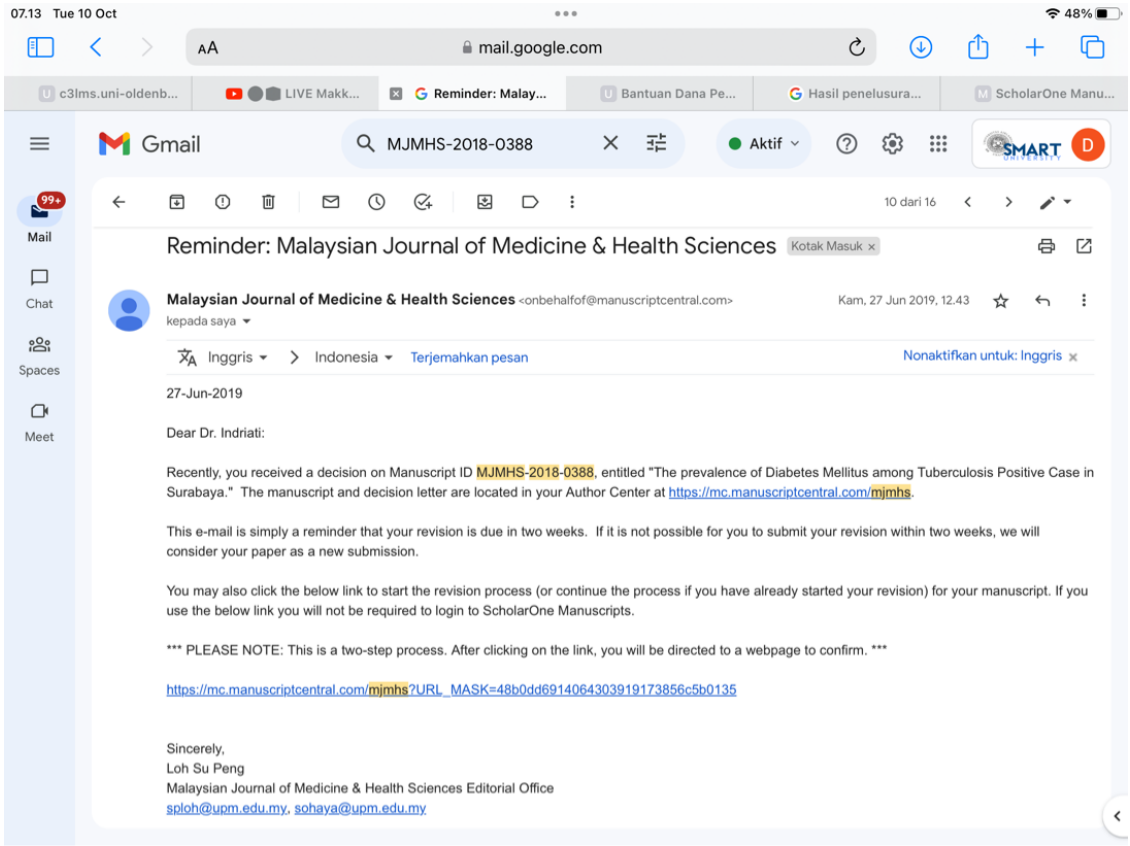
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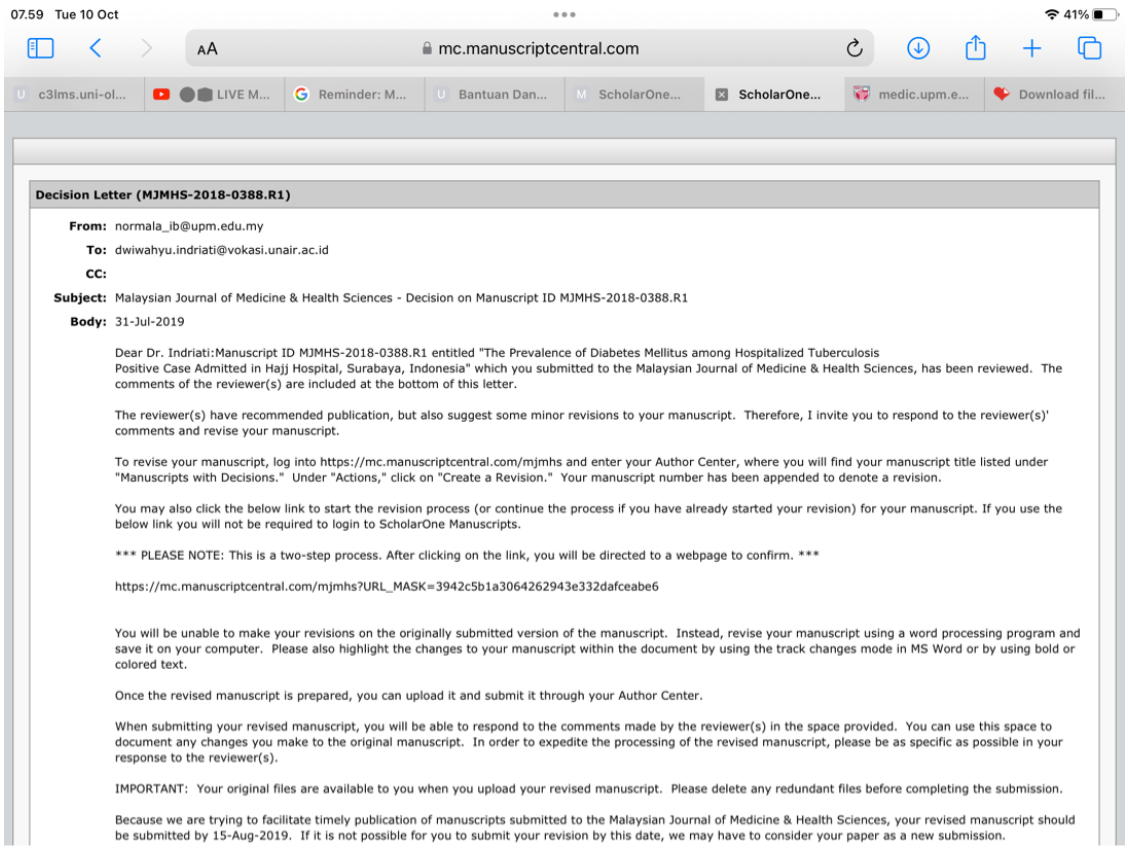
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The prevalence of Diabetes Mellitus among Tuberculosis Positive Case in Surabaya

Journal:	*Malaysian Journal of Medicine & Health Sciences*
Manuscript ID	MJMHS-2018-0388
Manuscript Type:	Original Article
Keywords:	Tuberculosis, Diabetes mellitus, HbA1c, PPG, FBG

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ABSTRACT

Introduction : Tuberculosis (TB) is the cause of significant health and death problems worldwide. Indonesia is known as the second largest country with TB burden in the world after India. The incident of TB is further increasing in diabetes mellitus patient. Diabetes mellitus disrupts the body's immune function, so patients are more susceptible to infection, including TB. The purpose of this study was to determine the prevalence of diabetes mellitus history (DM) among newly diagnosed TB patients in Surabaya. Materials and Methods: 160 patients were grouped into two groups, the first group, 67 patients were positive for TB and diabetes mellitus, 93 patients were positive for TB only. Data were collected from TB patients based on acid-fast bacilli stain (AFB) and positive Xpert MTB/RIFF. Blood glucose level were collected from post prandial, after fasting blood sugar level also glycated haemoglobin (HbA1c). Results: The prevalence of TB related with DM history was 42% from 55 ± 9.52 years old. Patient with TB-DM showed poor glucose blood level, their PPG was 268.61 ± 127.13 mg/dl, PPG level was 217.43 ± 99.20 mg/dl and the HbA1c result (> 6.5%) were 82%. The rifampicin resistant level result were not significantly different between TB and TB-DM (4.4% and 3% respectively). Conclusions : Our results highlight that poor diabetic control were determinant factors of TB susceptibility in DM patients. Therefore, a concerted effort is needed to treat this dual epidemic for a better outcome in Indonesia.

Keywords : Tuberculosis, diabetes mellitus, Rapid Test, HbA1c, rifampicin sensitive.

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INTRODUCTION

grammatical mistake

Tuberculosis has remain caused a global health problem. Tuberculosis caused by Mycobacterium tuberculosis. These bacteria are known as slowly growing bacteria which is also known as a single infectious agent that can include one of the top 10 causes of death worldwide. In 2017, it was estimated around 10 million patients infected with TB and 1.6 million patients have died (1). Indonesia has ranked second in the highest burden TB, and TB cases in Indonesia never reduce since many cases were undetected if its detected and cured but still any report regarding this kind of cases. Based on data by the Ministry of Health on 2017, 360.700 cases were found to be TB positive, and among them,168.412 cases were acid-fast bacilli smear-positive (2). At the same time, Indonesia also has a high burden for diabetes. According to Ministry of Health diabetes prevalence in adult (2013) around 6.9%. These numbers reduce to 6.3% in 2017, Indonesia has been listed as rank seven for diabetes prevalence in the world (3). The bidirectional association between TB and DM is one of the significant concern worldwide while the correlation between diabetes and tuberculosis remains debated. (reference ?)

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Diabetes mellitus (DM) is categorised as a metabolic disease with a specific characteristic of chronic hyperglycemia due to abnormalities in insulin secretion, insulin action or both which lead to high blood glucose levels (hyperglycemia). Patient with diabetes showed impaired innate immune system caused by the high level of blood glucose (4). Diabetes can disrupt the activation and function of macrophages, monocytes, lymphocytes, pulmonary microangiopathy, renal dysfunction and vitamin deficiency. Patient with poor control of hyperglycemia more susceptible to TB infection compared to a patient with good control of hyperglycemia (5). Prevalence of TB ~~was increased~~ increases threefold in people with diabetes (6). Thus it is necessary to monitor the prevalence of TB infection in DM patient in Surabaya.

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The objective of the present study was to describe the prevalence of TB incident in patients with DM history. These data are necessary to raise awareness in an attempt to reduce the susceptibility of TB from DM patient and reduce mortality rate caused by these dual epidemics. Tuberculosis infection among diabetes mellitus patients in Indonesia is still interested since now Indonesia has faced a double threat not only from TB but also DM.

In Materials and Method your objective is to check prevalence of DM among TB positive patients while in objective you are saying opposite. Please explain or correct???

MATERIALS AND METHODS

This study was conducted using an observational, analytical cross-sectional method. These studies were performed using secondary data from a medical record. Data were collected from 160 patients appointed in General Hospital Hajj, Surabaya from January-December 2017. All patient were TB positive. Inclusion criteria were set, a patient with all gender and all age, positive TB which were confirmed by sputum smears positive for Acid Fast Bacteria (AFB), or were confirmed by rapid diagnostic tests such as Xpert MTB/RIF only or sputum smears positive for AFB and positive with a rapid diagnostic test such as Xpert MTB/RIF. All patients were verified with DM history. Diabetes positive were confirmed with a random blood sugar of greater than 200mg/dl, fasting plasma glucose higher than 126 mg/dl and glycated haemoglobin (HbA1c) of greater than 6.5% before taking anti-tuberculosis therapy. All data were statistically analysed (descriptive and analytical statistics). which version of SPSS or excel?

RESULTS

Sputum Smear and Xpert MTB/RIF Combination Method Result in Higher Detection of Patient with Positive Tuberculosis

Among 160 patients, combinations method by using sputum smear and Xpert MTB/RIF yield a higher result in detecting tuberculosis positive. (Table 1). From the male and female patient, a combination of Xpert MTB/RIF and sputum smear resulted in 53% detection while sputum

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smear (15%) and Xpert MTB/RIF (31.88%). Our analysis found that detection methods have no significant difference in detecting patient for TB regarding their gender ($\chi 2 = 0.7$ with p= 0.7). Though it was noticed that there was male predominance in TB and TB-DM infection (male 86 patients while female 74 patients) but there were no significant differences in regards of patient gender between a female and male patient ($\chi 2 = 1$ with p= 0.75). This Xpert MTB/RIF is known as a highly sensitive and specific new tool for detecting TB and also for determining resistance to rifampicin. While 5% mono-resistance to rifampicin, a high proportion of those were now associated with resistance to isoniazid (~95%). Then by detecting resistance to rifampicin can also include Multiple Drug Resistance (MDR)-TB with high accuracy (7,8).

The prevalence of TB infection among patient with DM.

From 160 patients with TB, later found from medical record that 67 patients (42%) among them known to have diagnosed with Diabetes mellitus. Smear sputum result (smear sputum method only or smear sputum and Xpert MTB/RIF) showed that 47 patients (45.6%) with DM and other 56 patients (54.4%) without DM have smear sputum positive. Smear sputum result showed that both TB and TB-DM patient were positive 2 according to International Union Against Tuberculosis and Lung Disease (IUATLD) scale (Figure 1). From Xpert MTB/RIF result (Xpert MTB/RIF only or Xpert MTB/RIF and smear sputum) showed that 53 patients (39%) with DM and other 83 patients (61%) without DM showed a positive result for TB (Table 4).

Our results showed that there were no significant differences between female and male infected with TB only (female 56.76% and male 59.30%) or TB and DM history (female 43.24% and male 40.70%) (Table 2). The rate of TB infection was observed high in men compared to women, these results were observed from early epidemiology studies. It is often believed that

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male dominance in TB infection is caused by underdiagnosis of TB cases in women (9). One may suggest that female exhibit more-robust immune response to antigenic challenges than man (10). Thus it is convinced that those rules also accounted for TB infection.

The mean age of TB and TB-DM patients were 42 ± 17.24 years and 55 ± 9.5 years old respectively (Table 3, Figure 2). Our results showed there were significantly different since patient age variance among TB were greater compared to those data from TB-DM patients. Similar results also showed TB-DM patients mean age was 53 years vs TB patient 44 years (11) These results were often seen as DM type 2 is more prevalent in older age.

DM patient has poor diabetes control

Diabetes mellitus patient was presented with bad control of glucose blood level. Post-prandial blood glucose (PPG) in TB-DM patient was 268.61 ± 127.13 mg/dl (N=59, Figure 3a) while in TB patient was 126.41 ± 83.25 mg/dl (N=29, no statistical comparison due to insufficient data presented from TB patient). Fasting blood glucose level among TB-DM patient was 217.43 ± 99.20 mg/dl (N=51, Figure 3a). Hemoglobin A1c (HbA1c) level for TB-DM was 10.8 ± 3.25 % (Figure 3b). These results show poor glycemic control as a risk factor for TB infection in DM patients. Other studies in Indonesia also show the mean fasting blood glucose level among TB-DM was 215 (154-290) mg/dl (12).

Rifampicin resistance among TB and TB-DM patients

Rifampicin resistance/sensitive test showed that among 136 patients who diagnosed with Xpert MTB/RIF method, 126 patients (92.6%) showed sensitive to rifampicin while others ten patients (7.4%) showed resistance to rifampicin. Group of TB-DM patient showed 3% resistance to rifampicin. These number also quite similar to the group of TB patient showed resistance to rifampicin (4.4%) (Table 4). Rifampicin resistant TB (RR-TB) can be defined as

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resistant to rifampicin with or without resistance to other first-line anti TB drugs using genotypic or phenotypic methods. Multidrug resistance TB (MDR-TB) can be caused by Mycobacterium tuberculosis that is resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs. MDR-TB is treatable but costly and requires long time treatment with potentially toxic drug (13).

DISCUSSION

This study was conducted to evaluate the prevalence of diabetes mellitus infection among patient with confirmed TB positive patient in Hajj General Hospital, Surabaya Indonesia between January-December 2017. Patients that were confirmed tuberculosis positive using smear sputum and Xpert MTB/RIF or positive using smear sputum only and Xpert MTB/RIF only. Later we found several patients had diabetes mellitus history. The prevalence of diabetes mellitus among tuberculosis positive case was 42% among patient in 55 ± 9.52 years old. This number is high considering the previous study showed that the prevalence of DM among TB patients was 13.2% (14) and 14.8% (12). These discrepancies probably due to different sample size from the previous study (400-600 patients from the previous study).

The previous study by Alisjahbana et al. in 2007 stated that DM was associated with more symptoms but not with increased severity of TB. Our recent study did not address this issue, and our study wants to emphasise that DM patient with poor control of their diabetes can increase their prevalence of TB infection. Other study showed that DM patient has three times the chance of developing TB compared to the non-DM population (15-17). Although TB is believed to be strongly associated with immune deficiency disease such as HIV but the number of people infected with DM is much higher than that of immunocompromised states make it prominent factor associated with TB at the population level (18).

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The correlation mechanism between DM and TB are still in need of detailed investigation. There is no clear explanation on why people with DM more prone to TB compare to people with no DM. In Asian countries in which TB and DM have coexisted as a dual burden in those countries, these dual diseases can exist probably as a result of external (poor glycaemic control) and internal factors (specific mechanisms of insulin resistance, genetic susceptibility to DM (19).

Our result showed DM patient with PPG ± 127.13 mg/dl, fasting blood glucose level 217.43 ± 99.20 mg/dl and HbA1c level of 10.8 ± 3.25 % was susceptible to TB infection. Our result showed similarities with another result from Diabcare-Asia project which conduct the cross-sectional survey from 24,317 patients from Bangladesh, China, India, Indonesia, Malaysia, Philipines, Singapore, Sout Korea, Sri Lanka, Taiwan, Thailand, Vietnam found that among diabetic patient 55% had HbA1c level exceeding 8% (20). Persistent hyperglycaemia in DM patient can alter the immune response to Mycobacterium tuberculosis (Mtb). This alteration was associated with changes in the innate and cellular cytokine response to Mtb (21). Thus DM patient has a reasonable reason in increasing its risk to TB infection.

Other concerns arise from multiple drug resistance- tuberculosis (MDR-TB) cases to rifampicin. The data from WHO estimates that 3.9% of all new TB cases had MDR-TB or rifampicin-resistant TB (22). Our result also showed 4.4% new TB cases and 3% new TB cases among DM patients had MDR-TB. These result is contradicting the previous result that showed patient with DM and recently diagnoses positive for TB has an increased risk of MDR-TB case (23). Several studies have conducted to address the correlation between MDR-TB prevalence in TB and TB-DM patient, but all studies did not provide consistent evidence on whether DM has an increased risk for MDR-TB (24-26).

Most cases of MDR-TB are emerged from a mixture of physician error, inadequate and incomplete treatment, patient non-compliance during treatment of susceptible TB (27,28).

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While the correlation between increasing number of MDR strains of Mtb in a TB-DM patient can be explained by the association of poor glucose control and dysfunction of phagocytosis, reactive oxygen species (ROS) production, chemotaxis and T-cell reaction in DM patients (29). The other reason seems caused by less virulent MDR strain of Mtb is more likely to flourish in an immunocompromised patient with DM (30,31).

Our result suggests that initial screening for the newly diagnosed patient with TB for its correlation with DM history is important. Thus that information will be useful in choosing TB treatment while considering the risk of DM interference in TB therapy. Patient with DM was also encouraged to control their diabetic level to avoid other infection such as TB.

CONCLUSION

This study showed 42% prevalence of Diabetes Mellitus history in recently diagnosed TB patients in Surabaya. Factors determinants of TB in DM patients are uncontrolled diabetes, these are not factors ~~high rates of HbA1c, fasting glucose and postprandial glucose level.~~ Indonesia is widely recognised to have the dual epidemic burden, TB and DM, therefore, a concerted effort is needed to treat this dual epidemic for a better outcome.

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Figure Legends

Figure 1. Distribution of smear sputum result based on IUATLD scale. TB and TB-DM patient were categorised as positive one was found significantly higher as compared to other scales. Scanty means 1 to 9 AFB in 100 fields ; Positive 1 means 10 to 99 AFB in 100 fields ; Positive 2 means 1 to 10 AFB per fields in at least 50 fields ; Positive 3 means > 10 AFB per field in at least 20 fields.

Figure 2. Distribution of TB and TB-DM as regards of patient age. Scatter plot to show all data. The bars show the mean for each group meanwhile the error bars represent +/- standard deviation.

Figure 3. Comparison between the two groups (TB and TB-DM) as regards PPG, FBG and HbA1c. A, PPG usually measured glucose level (mg/dL) in the blood after a meal. While FBG usually measured glucose level (mg/dL) after fasting for 8 hours before test. Scatter plot to show all data. The bars show the mean for each group meanwhile the error bars represent +/- standard deviation. B, Glycated hemoglobin (A1C, in percentage) showed the precentage of blood sugar attached to hemoglobin (data was collected from TB-DM patient only). Data are given as means

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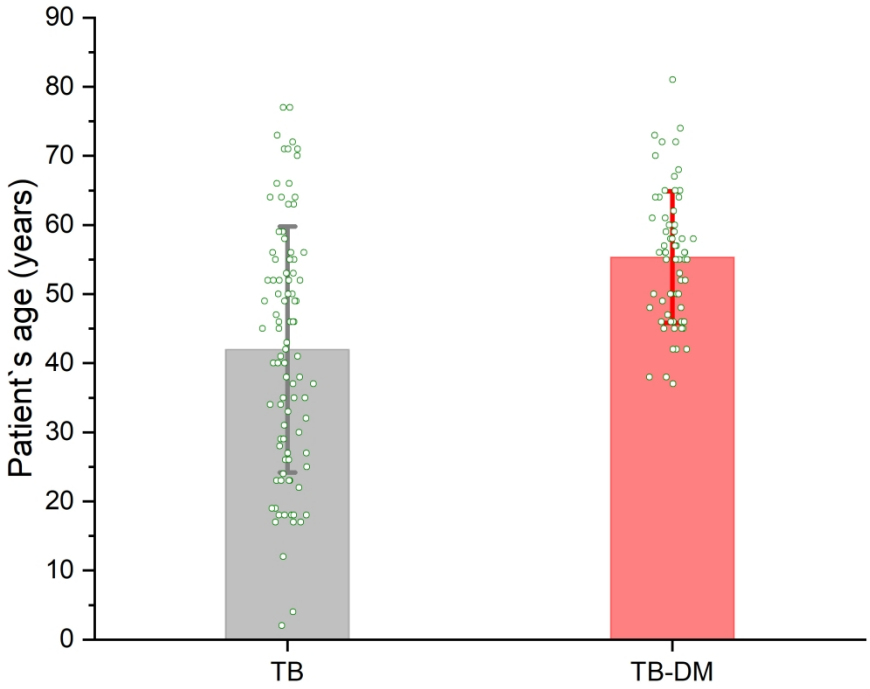

Figure 2. Distribution of TB and TB-DM as regards of patient age.

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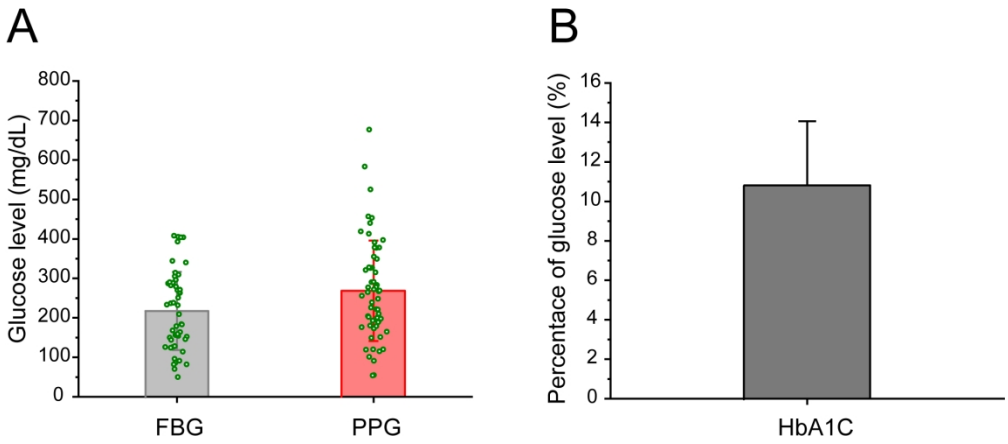

Comparison between the two groups (TB and TB-DM) as regards PPG, FBG and HbA1c.

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Table I. Distributed of TB positive cases as regards different methods of identification

		Sputum Smear	Xpert MTB/RIF	Sputum Smear and Xpert MTB/RIF	Total	Chi Square	#p
Gender						0.7	0.70
Female	No	13	23	38	74		
	%	17.57	31.08	51.35	100		
Male	No	11	28	47	86		
	%	12.79	32.56	54.65	100		
Total	No	24	51	85	160		
	%	15	31.88	53.13	100		

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Table 2. Distributed of TB and TB-DM cases as regards patient gender

		TB	TB-DM	Total	Chi Square	#p
Gender					1	0.75
Female	No	42	32	74		
	%	56.76	43.24	100		
Male	No	51	35	86		
	%	59.30	40.70	100		
Total	No	93	67	160		
	%	58.13	41.88	100		

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Table 3. Distributed of TB and TB-DM cases as regards patient age

Group	N	Mean	SD ±	T test
Age				1.02309E-08
TB	93	41.98	17.79	
TB-DM	65*	55.34	9.52	

*2 patients age was unknown

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Table 4. Distributed Xpert MTB/RIF result among TB and TB-DM patients

Xpert MTB/RIF	TB-DM	TB	Total
MTB/RIF SENSITIVE	49 (36%)	77 (56.6%)	126 (92.6%)
MTB/RIF RESISTEN	4 (3%)	6 (4.4%)	10 (7.4%)
Total	53 (39%)	83 (61%)	136 (100%)

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Prevalence of Diabetes Mellitus amg tuberculosis positive cases in Surabaya

The topic is interesting and would have contributed to scientific knowledge if authors could reply the major commnets.

General:

1. Authors need to send the manuscript for proof reading as there were many grammatical mistakes
2. Authors need to understand the limitations of this study. The authors were discussing facts that were beyond the scope of this study design and sample selected.
3. Authors did not describe limitations of this study. The prevalence of diabetes mellitus among TB patients in this study was very high compared to other local studies in Indonesia. This could be contributed because the study chose only hospitalised patients. TB patients are usually hospitalised because they are quite ill, not responding to treatment, has co-morbid conditions or has complications.

Title:

1. It is inaccurate to generalised this study for TB in Surabaya as the study was conducted only among patients admitted in General Hospital Hajj. In Methodology, the authors did not mention any sampling to select hospitals or health clinics to represent Surabaya. Author may need to consider changing the title to prevalence of DM among hospitalised TB positive cases for reasons elaborated in **General comment #3**

Abstract:

1. Author should rephrase Indonesia is known as the second largest country with TB burden. The correct way to describe burden is by using highest or lowest. Largest refers to land area.
2. Conclusion made by authors did not summarize the objective of the study and is beyond the scope of this study. Should the authors insist on that conclusion, they have to revise the sample size and presentation of results.

Materials and Methods:

1. It is sufficed to mention that “A cross sectional study was conducted at General Hospital Hajj, Surabaya between January to December 2017.”

Results:

1. Authors should first describe overall demographics of study sample by groups TB with DM and TB without DM.
2. Authors do not need to write down everything that has been described in the Tables. Just highlight the important results and necessary significant or nonsignificant findings.
3. Tables can be presented with number of cases and percentages side by side i.e. n (%) for easier viewing and Table 2, 3 and 4 can be merged into one Table.
4. Authors should not include comparison with other studies in the Results Section.
5. Under subsection DM patient has poor diabetes control, authors should present number and percentage of cases with good control and number and percentage of cases with poor control rather than just the mean and SD levels

Discussion:

1. **The authors should delete the first three sentences in Paragraph 1 of Discussion. Not necessary to repeat what was already described in Methodology.**
2. **Do not also repeat the figures (numbers, percentages, mean and SD etc) that have been stated in Results section.**
3. Most of what was discussed in Discussion Section could not be addressed by this study as the study design was not proper to answer the questions raised. Example: our study wants to emphasise that DM patient with poor control of their diabetes can increase their prevalence of TB infection. Authors will need to actually prevalence of TB among patients with good DM control and compare it with prevalence of TB among patients with poor DM control.
4. Error was again made in Paragraph 3: authors stated "Our result showed DM patient with PPG 268.61 ± 127.13 mg/dl, fasting blood glucose level 217.43 ± 99.20 mg/dl and HbA1c level of 10.8 ± 3.25 % was susceptible to TB infection." How could authors of this study conclude this statement when they did not show percentage of Diabetics with TB was actually less than TB patients without DM?

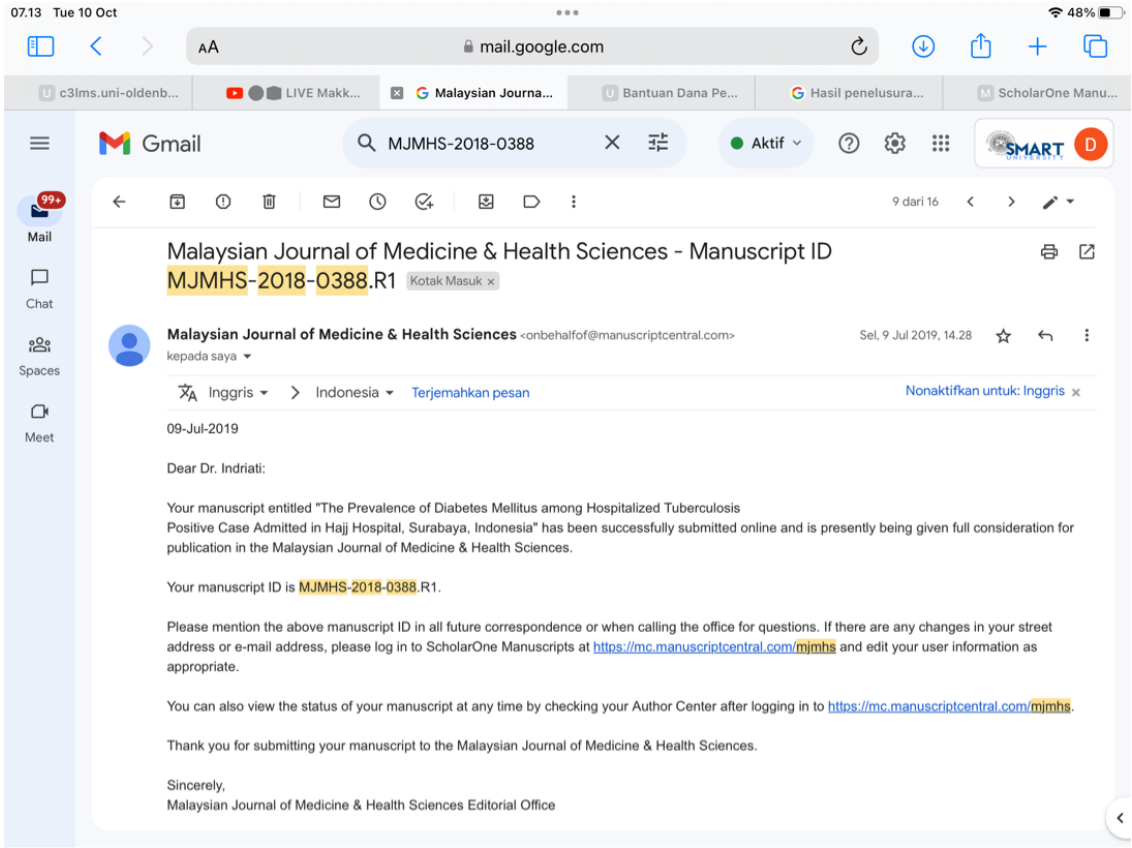
Conclusion:

Comment has already been made earlier in Abstract

BUKTI KORESPONDENSI
ARTIKEL JURNAL INTERNASIONAL SCOPUS Q4

Judul artikel: The prevalence of Diabetes Mellitus among Tuberculosis Positive Case in Surabaya
Jurnal : Malaysian Journal of Medicine and Health Science, 16 (1)
Author : Putri, E.I.S; Indriati, D.W & Wahyunitisari M.R.

No	Perihal	Tanggal
3	Bukti pengiriman revisi I	09 Juli 2019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Your manuscript entitled "The Prevalence of Diabetes Mellitus among Hospitalized Tuberculosis Positive Case Admitted in Hajj Hospital, Surabaya, Indonesia" has been successfully submitted online and is presently being given full consideration for publication in the Malaysian Journal of Medicine & Health Sciences.
Your manuscript ID is MJMHS-2018-0388.R1.
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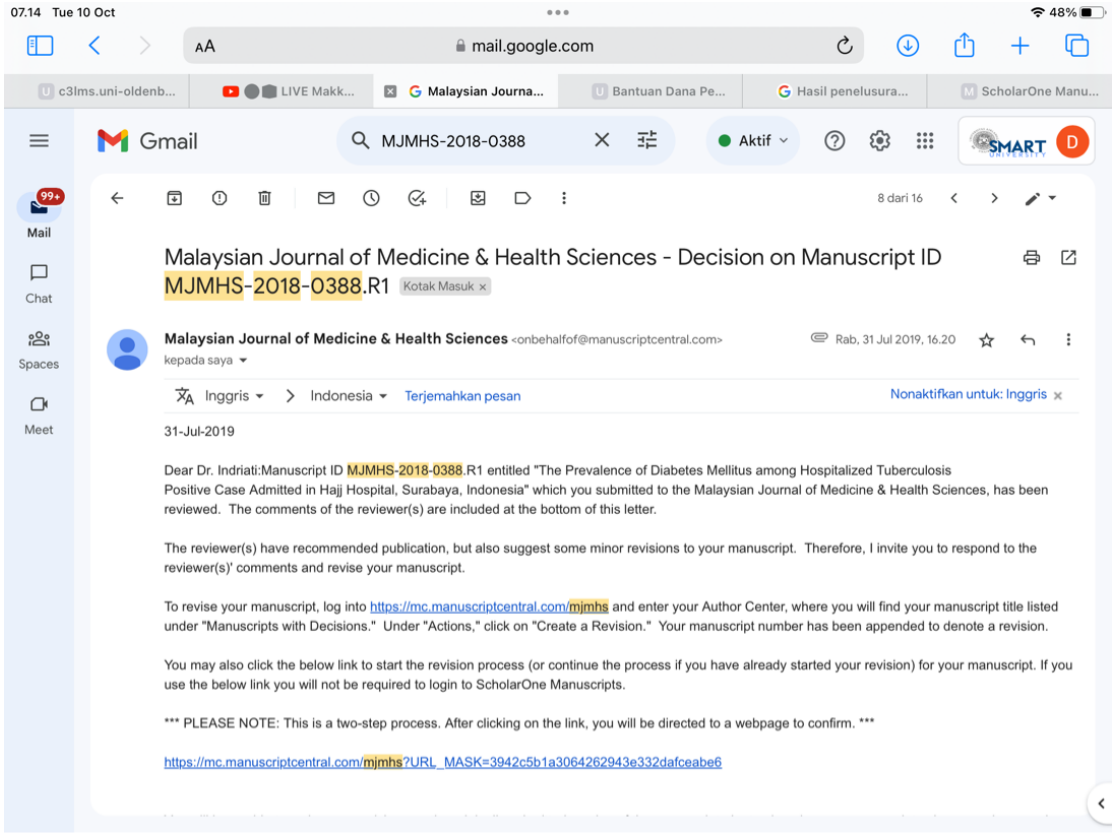
Jurnal : Malaysian Journal of Medicine and Health Science, 16 (1)
Author : Putri, E.I.S; Indriati, D.W & Wahyunitisari M.R.

No	Perihal	Tanggal
4	Bukti pengiriman review II	31 Juli 2019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The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.
To revise your manuscript, log into https://mc.manuscriptcentral.com/mjmhs and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.
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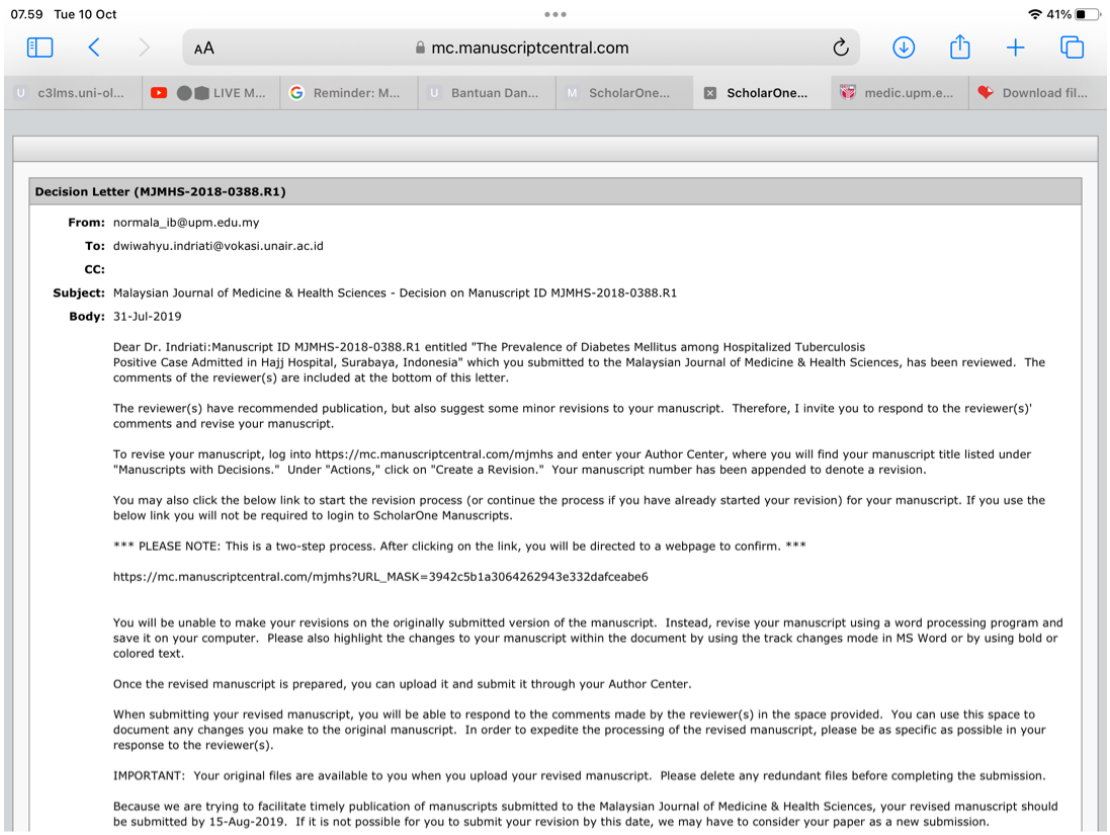
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Decision Letter (MJMHS-2018-0388.R1)
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CC:
Subject: Malaysian Journal of Medicine & Health Sciences - Decision on Manuscript ID MJMHS-2018-0388.R1
Body: 31-Jul-2019
Dear Dr. Indriati:Manuscript ID MJMHS-2018-0388.R1 entitled "The Prevalence of Diabetes Mellitus among Hospitalized Tuberculosis Positive Case Admitted in Hajj Hospital, Surabaya, Indonesia" which you submitted to the Malaysian Journal of Medicine & Health Sciences, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.
The reviewer(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.
To revise your manuscript, log into https://mc.manuscriptcentral.com/mjmhs and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.
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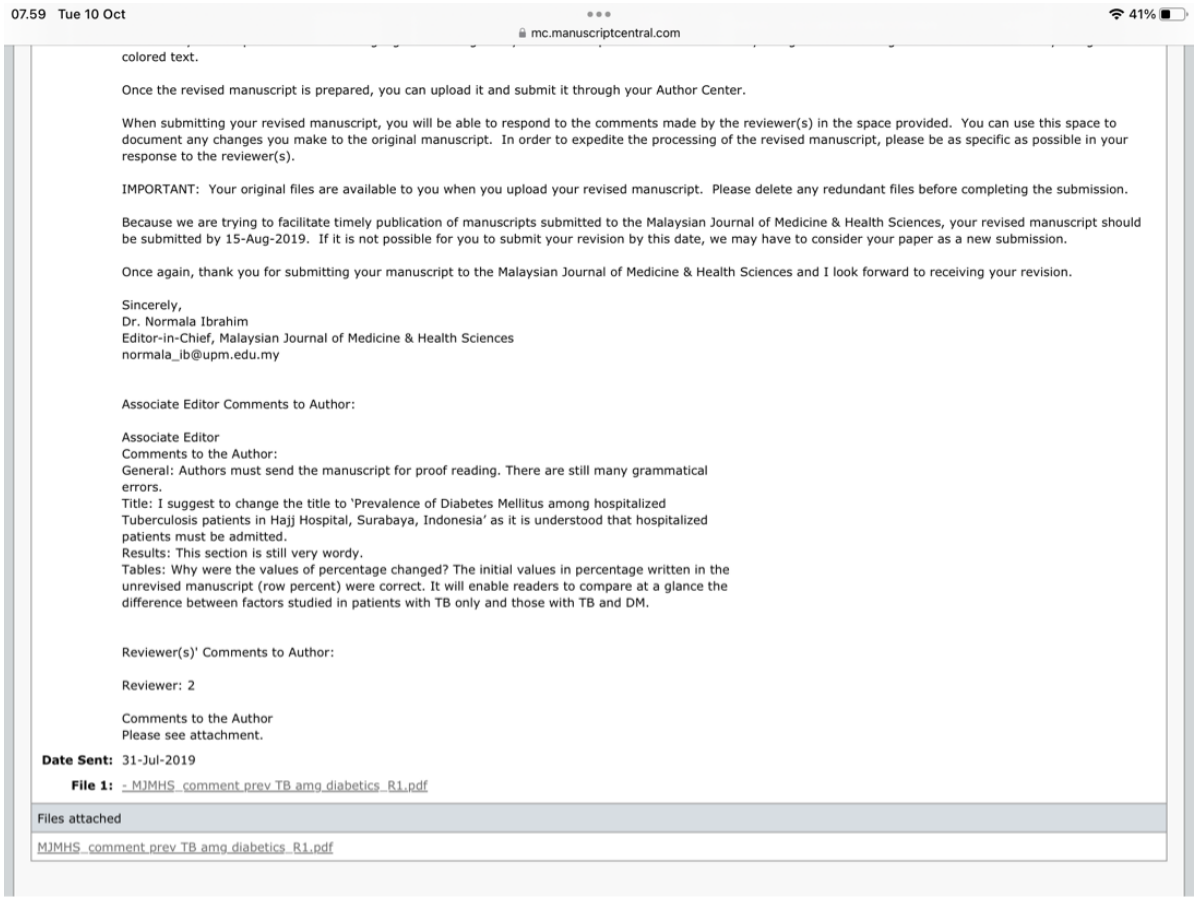
Because we are trying to facilitate timely publication of manuscripts submitted to the Malaysian Journal of Medicine & Health Sciences, your revised manuscript should be submitted by 15-Aug-2019. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.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Once again, thank you for submitting your manuscript to the Malaysian Journal of Medicine & Health Sciences and I look forward to receiving your revision.

Sincerely,
Dr. Normala Ibrahim
Editor-in-Chief, Malaysian Journal of Medicine & Health Sciences
normala_ib@upm.edu.my

Associate Editor Comments to Author:

Associate Editor
Comments to the Author:
General: Authors must send the manuscript for proof reading. There are still many grammatical errors.
Title: I suggest to change the title to 'Prevalence of Diabetes Mellitus among hospitalized Tuberculosis patients in Hajj Hospital, Surabaya, Indonesia' as it is understood that hospitalized patients must be admitted.
Results: This section is still very wordy.
Tables: Why were the values of percentage changed? The initial values in percentage written in the unrevised manuscript (row percent) were correct. It will enable readers to compare at a glance the difference between factors studied in patients with TB only and those with TB and DM.

Reviewer(s)' Comments to Author:

Reviewer: 2

Comments to the Author
Please see attachment.

Date Sent: 31-Jul-2019

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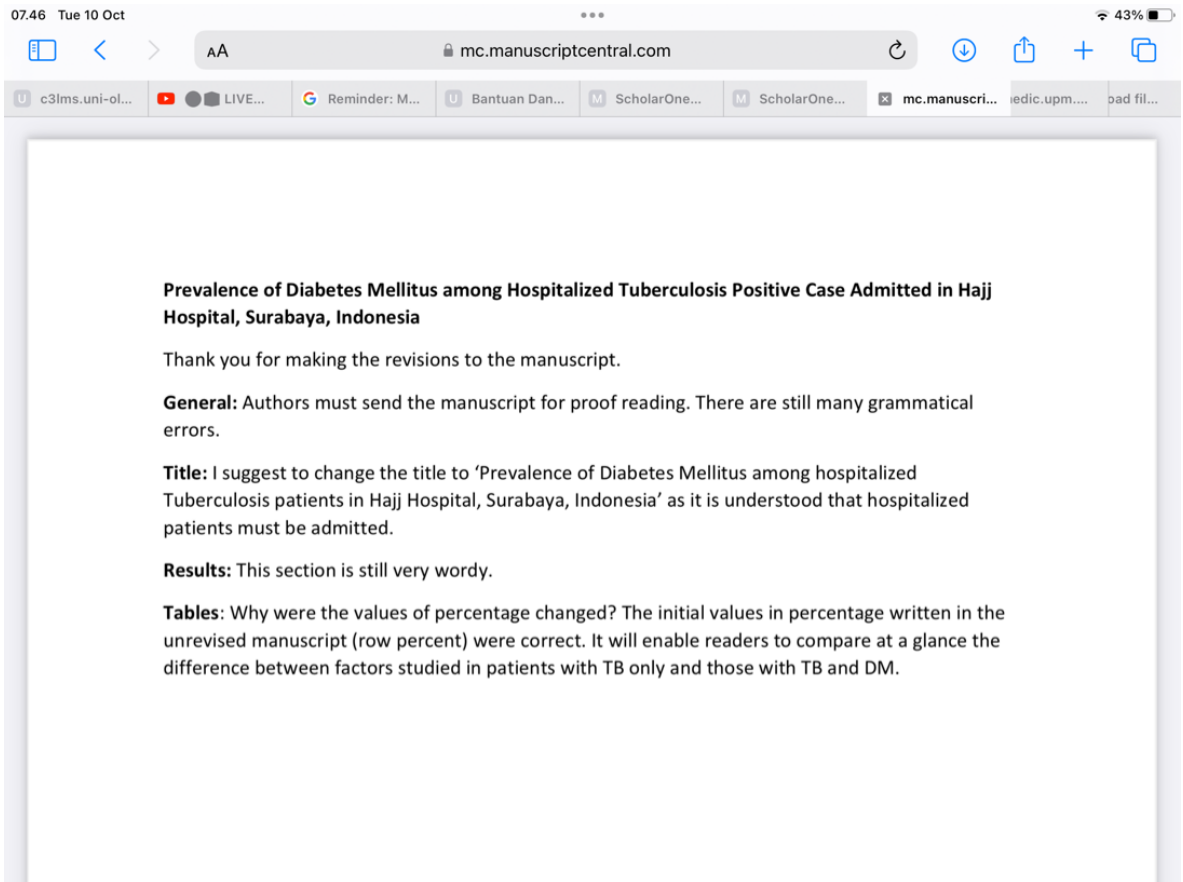
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Prevalence of Diabetes Mellitus among Hospitalized Tuberculosis Positive Case Admitted in Hajj Hospital, Surabaya, Indonesia

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Jurnal : Malaysian Journal of Medicine and Health Science, 16 (1)
Author : Putri, E.I.S; Indriati, D.W & Wahyunitisari M.R.

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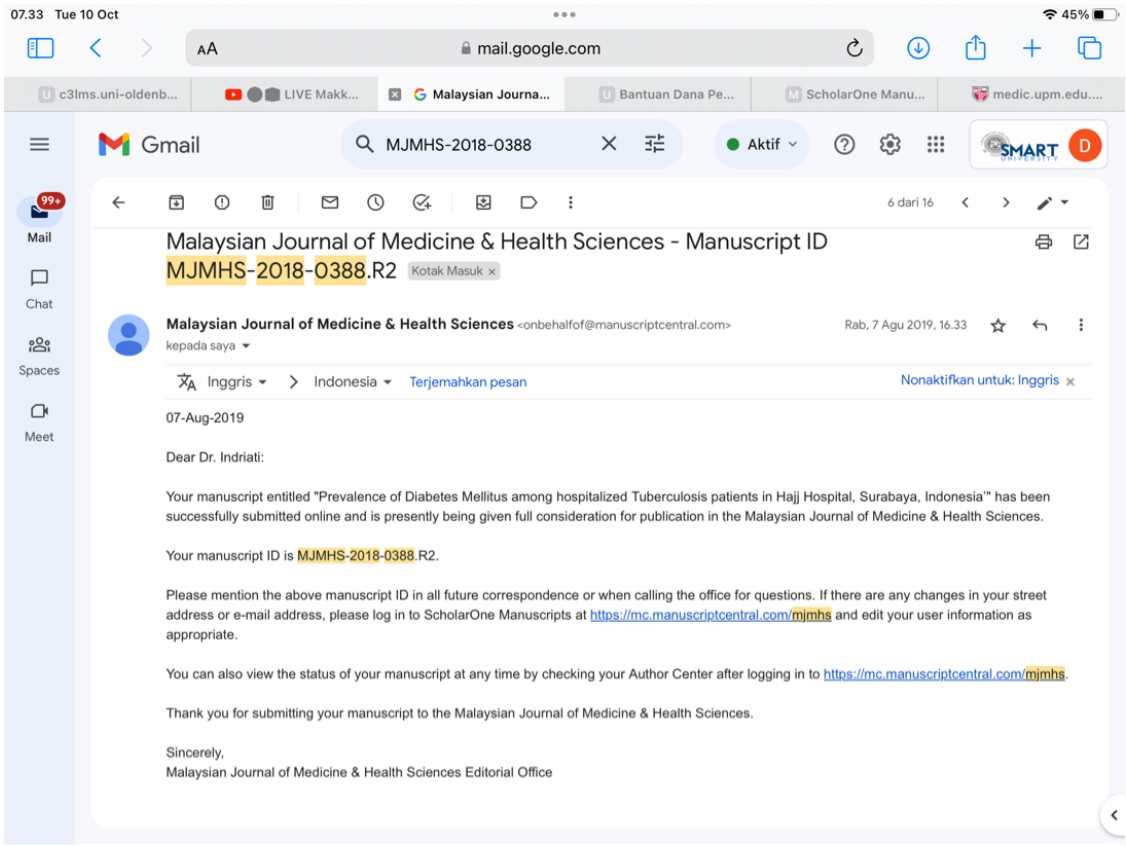
5	Bukti pengiriman revisi II	07 Agustus 2019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Author : Putri, E.I.S; Indriati, D.W & Wahyunitisari M.R.

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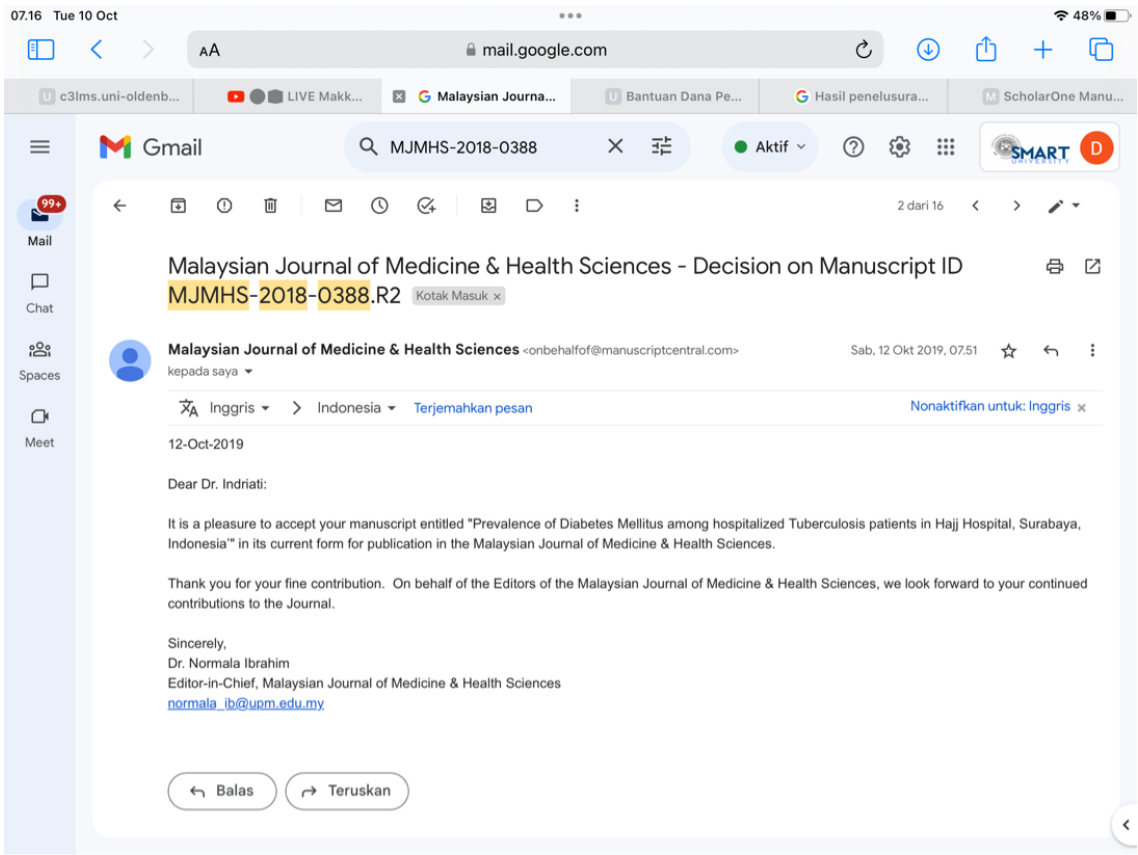
6	Bukti penerimaan artikel	12 Oktober 2019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12-Oct-2019
Dear Dr. Indriati:
It is a pleasure to accept your manuscript entitled "Prevalence of Diabetes Mellitus among hospitalized Tuberculosis patients in Hajj Hospital, Surabaya, Indonesia'" in its current form for publication in the Malaysian Journal of Medicine & Health Sciences.
Thank you for your fine contribution. On behalf of the Editors of the Malaysian Journal of Medicine & Health Sciences, we look forward to your continued contributions to the Journal.
Sincerely,
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Editor-in-Chief, Malaysian Journal of Medicine & Health Sciences
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