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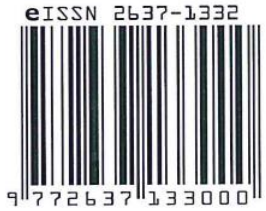

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Impact of Pharmacist Intervention Using MEDS-UOD on Medication Adherence among Schizophrenia Patients

Siti Fatimah Samat[1], Khai Sin Choong[1], Umi Solehah Sa'ad[1], Nurlaila Baharudin[1]

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Abstract

Introduction: About 80% of patients with schizophrenia were found non-adherent towards antipsychotic medications at some stage of their illness. Medications-Unit of Dose (MEDS-UOD) was an intervention by the pharmacists to improve medication adherence among schizophrenia patients.

Objective: To evaluate the impact of pharmacist intervention using MEDS-UOD on medication adherence in schizophrenia patients.

Method: This study was conducted using quasi-experimental study design. Patients with schizophrenia who received treatment at the Psychiatric Clinic of Hospital Melaka between January to December 2018 were recruited. Patients were divided into Control Group (CG) and Intervention Group (IG). CG patients received usual care, standard communication and standard counselling, while IG patients received MEDS-UOD booklet, refill reminder through phone call, and standard counselling. MEDS-UOD was a new packaging intervention in which individually packed medications were arranged according to prescribed dose and frequency in a booklet. Medication-adherence were measured using validated Medication Adherence Rating Scale (MARS) score and pill count (%) method at baseline, and three and five months after interventions.

Results: A total of 60 subjects had completed five months of follow ups (n=33 in CG versus n=27 in IG). Compared with CG, the pill count percentage significantly improved in IG at 3 and 5 months after intervention ($p<0.001$). However, no significant changes in MARS score were recorded between the two groups at all time of follow ups. In IG, the mean differences in both pill count percentage and MARS score between baseline and five-month post-intervention was statistically significant ($p<0.001$ and $p=0.020$ respectively).

Conclusion: MEDS-UOD could be a useful intervention to improve medications adherence among schizophrenia patients and could be recommended for schizophrenia patients with compliance issues.

Keywords: Medication adherence, pharmacist, schizophrenia, packaging intervention

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Introduction

Schizophrenia stands as a prevalent mental ailment, ranking among the top fifteen contributors to global disability, impacting around 21 million individuals (1). Those afflicted by schizophrenia encounter instances of hallucinations, delusions, disorganized speech, unpredictable behaviour and also exhibit negative symptoms. The middle occurrence rate of schizophrenia was recorded at 15.2 per 100,000 individuals (with a range of 7.7 to 43.0 per 100,000) (2). In Malaysia, the National Mental Health Registry for Schizophrenia which was established in 2003, documenting a total of 7351 cases that had been registered from year 2003 to 2005. This chronic and debilitating disease severely disrupts psychosocial functioning across various aspects of life. Thus, leading to significant economic burden due to reduced employability, productivity and escalating expenses linked to illness management (3).

Continued utilization of antipsychotic medications over an extended period is a crucial element of treatment for individuals diagnosed with schizophrenia (5). Unfortunately, those suffering from schizophrenia frequently exhibit incomplete adherence to the prescribed medication. According to the Malaysia Psychiatric Association, there were about 80% of patients with schizophrenia were found non-adherent towards the antipsychotic medications at some stage of their illness (4). Non-adherence towards antipsychotic medications is often divided into intentional and unintentional, though both can occur in the

same individual. Intentional non-adherence occurs when a patient deliberately decides not to take medication as prescribed. Examples of unintentional non-adherence include forgetting to take a dose of medication, misunderstanding medication directions, losing medication, and environmental barriers such as transportation issues (6). The consequences of non-adherence include relapse, treatment failure, increased morbidity, hospitalization, and increased healthcare costs (7). Hence, improved adherence may reduce relapse rates, decrease the length of hospital stay, and reduce healthcare costs (6).

Several specific interventions have been used to improve antipsychotic adherence, including psychosocial interventions, service interventions, education, integrated care, packaging and daily reminders and financial incentives. The distinction between these interventions is not absolute, and some studies use a combination of strategies (6, 8). These interventions needed an active engagement of healthcare resources due to their complexity and labour intensive nature, thereby resulting in increased costs (8). Recommendations for enhancing medication adherence have long involved packaging interventions that include various packaging formats. These formats aim to improve medication adherence by physically organizing medications in a manner that indicates the specific day and/or time for administration. Common examples of packaging interventions include professionally prepared blister packs, unit-packaging, unit-of-use systems and unit-of-dose packaging which provide correct medications in containers. . Meanwhile, medication interventions involving pill boxes may not demand professional involvement as patients, informal caregivers or healthcare providers can fill these pill boxes (9).

A study which implemented unit-of-use packaging medications had found positive finding to improve patient adherence that included all patient's medication for psychiatric and general medical conditions. In addition to the intervention, they providing educational sessions and timely refill reminders two weeks before scheduled refill dates where this approach offers a means for patients to independently monitor their medication intake. This methodology is particularly effective for medications that require consumption at distinct times throughout the day, as it eliminates the need for patients to decide which medications to take at different intervals (10). Despite being widely studied within Western countries, the inconsistency in the methodologies and outcomes still exists across studies, with varying approaches to the same interventions. These factors have hindered the attainment of conclusive evidence that could be directly applied to the healthcare context in Malaysia.On top of that, no data regarding impact of packaging intervention toward medication adherence among psychiatry patient in Malaysia. Thus, our objective of this study is to investigate patients' adherence towards antipsychotic medication through a pharmacist intervention using MEDS-UOD to compare the mean pill counts percentage and MARS score between different groups and to compare the mean differences of pill count percentage and MARS score in different time periods in Hospital Melaka setting.

Method

Recruitment

This study was conducted using a quasi-experimental design at Psychiatric Clinic Hospital Melaka between January to December 2018. Screening and recruitment of the patients was carried out at the Outpatient Pharmacy Department. Inclusion criteria were patients aged between 18 to 60 years, stable schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), who started antipsychotic drugs at least four weeks of treatment and those who took tablet preparations only. There were four features for exclusion criteria include those schizophrenia patients who were new to drug treatment, had cognitive impairment that may hinder the assessment, patients who received antipsychotic medications outside from Psychiatric Department Hospital Melaka and patient who had syrup or solution antipsychotic only. Participants who able to comprehend the study's objectives and expressed a willingness to provide their consent were enrolled.

Patients were alternately grouped into two groups which are the Control Group (CG) and the Intervention Group (IG) by order of recruitment. Patients in the control group received usual care which are the standard communication regarding their medications at the pharmacy and standard medication counselling. Any questions directed to the pharmacist were responded to in accordance with the standard procedures followed in the pharmacy. Meanwhile, intervention group patients received the MEDS-UOD intervention and standard medication counselling. All patients received standard medication counseling which followed the psychoeducation module established by the Ministry of Health Malaysia (11).

Sample size

Sample size was calculated using EpiCalc 2000 software. Based on a power of 80% (β=0.2), alpha of 0.05, an expected mean difference of MARS score is 10% and standard deviation of 4% between the 2 study interventions. The margin of error is 20% of the mean difference. Calculated sample size (N) for each group is 30 patients. Allowing for 10% dropout, a final sample size of 35 per group will be used.

MEDS-UOD

MEDS-UOD (Medications-Unit of Dose) was a new packaging intervention in which individually packed unit of dose (UOD) medications were arranged in a booklet according to the prescribed dose and frequency (Figure 1). For instance, the medication strips were cut into UOD and filled in a plastic zipper bag and stapled at the MEDS-UOD sheet according to the intake time and date. All sheets were compiled into a patient's booklet, which consists of a front page, patient medication summary and MEDS-UOD sheet for one month or until the next appointment. The booklet also has refill reminder. Each patient has to take one packed medication at one time according to the date written in the booklet. MEDS-UOD can be prepared early, before the patient's appointment at pharmacy, except during the recruitment phase.

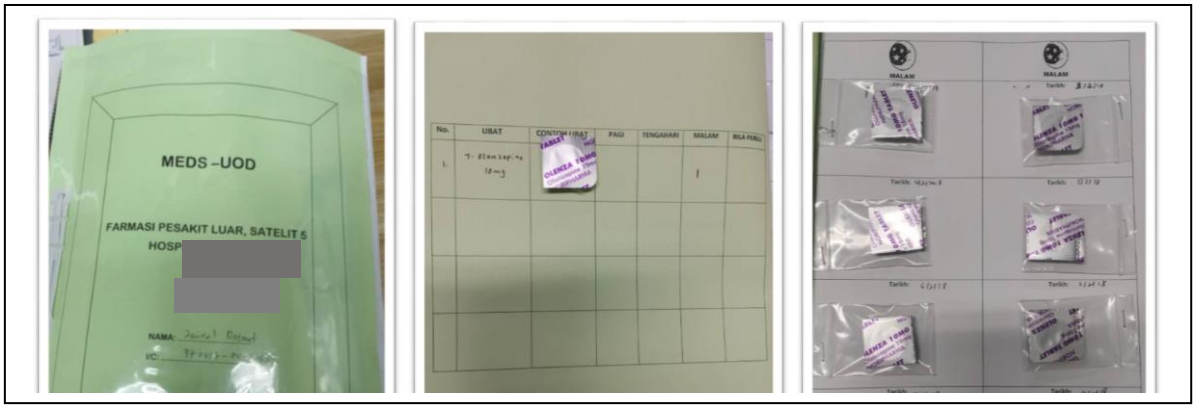

Figure 1: MEDS-UOD booklet

During the recruitment phase for the intervention group, patients were explained regarding the MEDS-UOD booklet. Those patients in the intervention group were called a week before refill dates to ensure patients came at scheduled appointment dates every month. Patients were asked to bring the MEDS-UOD booklet in an empty zipper plastic bag. All zipper plastic bags were recycled for next appointment at the pharmacy. The cost of MEDS-UOD booklet for each patient for once-daily dosing was RM3.60 over six months study; meanwhile, cost for twice-daily dosing was RM7.20 over six months.

Data Collection

The information was collected using a data collection form. Part A consisted of demographic data such as age, gender, race, marital status, education level, duration of illness, number of medications and employment status. Part B consisted of medication adherence assessment using the pill count method (%) and the validated Medication Adherence Rating Scale (MARS) score (12). The MARS score consisted of ten questions Yes/No scale which evaluated both attitudes about the medication and actual medication taking behavior. The total score ranges from zero (low likelihood of medication adherence) to ten (high likelihood of medication adherence). The questionnaires were self-administered. The pharmacist will answer the patient's queries when clarification is needed.

Both the English and Malay versions of the MARS were used in this study. Permission of using MARS in this study has been obtained from the authors. Medication adherence using MARS score and pill count (%) were assessed at baseline, three and five months after interventions. To measure pill count, the patient required some initial preparation, including asking patients to keep all empty medication blisters and empty zipper plastic bags. Equations of medication adherence measure using pill count used in this study as mentioned below (13).

$$PILL\ COUNT = \frac{(Number\ of\ dosage\ unit\ dispensed - number\ of\ dosage\ unit\ remained)}{(Prescribed\ number\ of\ dosage\ unit\ per\ day \times number\ of\ days\ between\ 2\ visits)} \times 100$$

Analysis

All data were analysed by using SPSS® program version 23.0 software. Descriptive statistics such as mean and standard deviation (SD) were used for continuous demographic variables. Categorical variables were summarised in frequency (n) and percentage (%). Kolmogorov Smirnov test showed the data were normally distributed, thus Repeated Measure ANCOVA was applied to compare the mean of MARS score and pill count (%) between groups. This method was used to identify which group has given a positive impact to improve medication adherence. Pairwise comparison (Bonferroni) of repeated measure ANOVA was applied to measure the mean differences of MARS score and pill count (%) between different time periods. This analysis was conducted to explore the time effect between these two groups and identify whether this measurement has changed in that duration. P-values less than 0.05 were considered statistically significant.

Ethics Statement

This study was registered in the National Medical Research Registry (NMRR) (NMRR-17-2766-36795) and approved by the MOH Medical Research and Ethics Committee (MREC). Informed consents were obtained from patients before enrolment into the study.

Results

A total of 112 patients were assessed for eligibility. After exclusion, only 69 patients were enrolled. However, only 60 of them completed the five-month follow-up period. There were 33 patients in the CG and 27 patients in the IG (Figure 2). The demographic characteristics of the subjects are shown in Table 1. The mean age of CG and IG was 41.5 (SD 8.8) and 36.9 (SD 8.7) years old, respectively. The majority of the subjects in CG were male (72.7%) and Malay (57.6%), while the majority of the subjects in IG were female (59.2%) and Chinese (55.6%).The duration of illness was similar for CG and IG, which were 12.5 (SD 10.6) and 13.0 (SD 9.1) years, respectively.

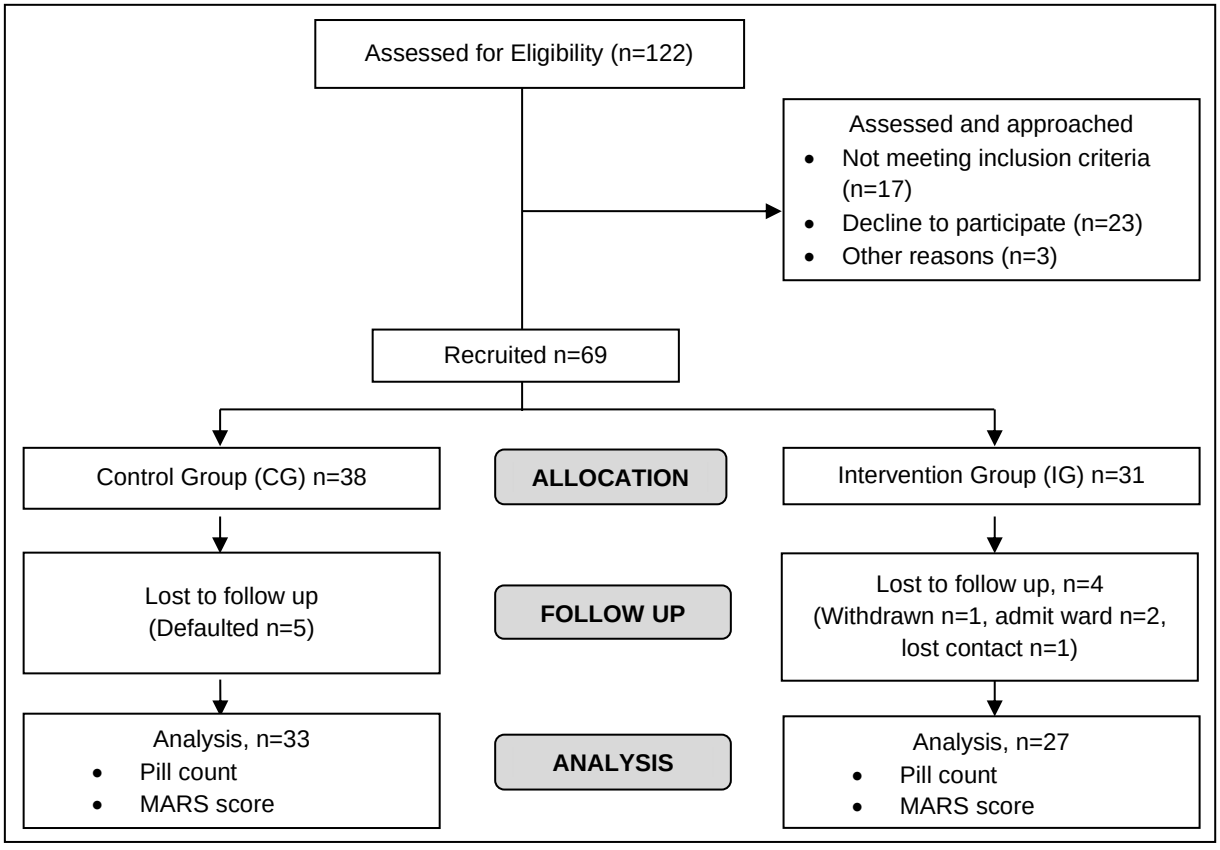

Figure 2: Flow chart of recruitment of the study population

Table 1: Demographic characteristic of the study population

Characteristic	Control Group (n= 33)	Intervention Group (n= 27)
Age (mean ± SD)	41.5 (8.8)	36.9 (8.7)
Gender		
Male	24(72.7)	11(40.7)
Female	9(27.3)	16(59.2)
Race		
Malay	19(57.6)	11(40.7)
Chinese	13(39.4)	15(55.6)
Indian	0	1(3.7)
Others	1(3.0)	0
Marital status		
Married	11(33.3)	5(18.5)
Single	20(60.6)	22(81.5)
Widow/widower	2(6.1)	0
Number of medication		
1	19(57.6)	15(55.6)
2	9(27.3)	8(29.6)
≥3	5(15.2)	4(14.8)
Employment		
Employed	14(42.4)	18(66.7)
Unemployed	19(57.6)	9(33.3)
Duration of illness (mean ± SD)	12.5(10.6)	13.0(9.1)

Abbreviation: SD = Standard deviation

Compared with CG, the mean (95%, Confidence Interval (CI) of pill count percentage was significantly higher in IG at 3 and 5 months after intervention [3 months:(97.5%(93.5-101.5) vs 89.5%(85.9-93.1)]; and 5 months:[100.2%(97.9-102.5) vs 92.3%(90.2-94.4); p<0.001] (Table 2). However, no significant changes in the mean (95%CI) MARS score were observed between both groups at all times of follow up (Table 3).

Table 2: Comparison of adjusted mean of pill count percentage between groups with adjustment of baseline

Month after intervention	Adjusted mean (95% CI)		F-statistics (df)	p-value
	Control Group (CG)	Intervention Group (IG)		
Baseline	87.9 (84.9, 90.9)	93.2 (89.8, 94.3)		
3 months	89.5 (85.9, 93.1)	97.5 (93.5, 101.5)	17.1 (1,57)	<0.001
5 months	92.3 (90.2, 94.4)	100.2 (97.9, 102.5)		

Repeated Measure ANCOVA [baseline adjustments] F(df) = 17.1 (1,57); p<0.001
Abbreviation: CI = Confidence interval; df = Degrees of freedom

Table 3: Comparison of adjusted mean of MARS score between Groups with adjustment of baseline

Month after intervention	Adjusted mean (95% CI)		F-statistics (df)	p-value
	Control Group (CG)	Intervention Group (IG)		
Baseline	8.5 (8.1, 8.8)	8.3 (7.4, 8.7)		
3 months	8.7 (8.3, 9.0)	8.9 (8.5, 9.3)	2.2 (1,57)	0.141
5 months	8.3 (7.9, 8.7)	9.1 (8.6, 9.5)		

Repeated measure ANCOVA [baseline adjustments] F(df) = 2.2 (1,57) ; p=0.141
Abbreviation: CI = Confidence interval; df = Degrees of freedom

In IG, the mean difference (95%CI) between baseline and 5 months intervention of pill count percentage [-7.6(-11.2 -4.0); p<0.001] and MARS score [-0.7(-1.4 -1.0); p=0.020] was found statistically significant (Table 4 & 5). No significant improvements were observed in CG group after 5 months.

Table 4: Comparison of changes in pill count percentage at different study time points

Comparisons (month after intervention)	Control Group (CG)		Intervention Group (IG)	
	Adjusted mean difference (95% CI)	p-value	Adjusted mean difference (95% CI)	p-value
Between baseline and month 3	-1.5 (-7.7, 4.6)	>0.95	-4.3 (-8.2, -0.4)	0.029
Between baseline and month 5	-3.8 (-8.2, 0.7)	0.127	-7.6 (-11.2, -4.0)	<0.001

Pairwise comparison (Bonferroni) of repeated measure ANOVA for each CG and IG.
Repeated measure ANCOVA [baseline adjustments] F (df) = 4.3 (1.5, 86.3), p=0.026)
Abbreviation: CI = Confidence interval

Table 5: Comparison of changes in MARS score at different study time points

Comparisons (month after intervention)	Control Group (CG)		Intervention Group (IG)	
	Adjusted mean difference (95% CI)	p-value	Adjusted mean difference (95% CI)	p-value
Between baseline and month 3	-0.1 (-0.6, 0.4)	>0.95	-0.7 (-1.3, -0.1)	0.023
Between baseline and month 5	0.2 (-0.3, 0.7)	0.886	-0.7 (-1.4, -1.0)	0.020

*Pairwise comparison (*Bonferroni) *of repeated measure ANOVA for each CG & IG.*
Repeated measure ANCOVA [baseline adjustments] F (df) = 2.4 (2,114), p=0.092
Abbreviation: CI = Confidence interval

Discussion

Medication adherence in mental health treatment is very important (14). Hence, intervention such as the MEDS-UOD was implemented as an adherence aid to educate schizophrenia patients about their antipsychotic treatment and emphasize compliance. The MEDS-UOD packaging utilized in our study differs slightly compared to one study where the packaging consisted of a seven-day supply of medications organized on a strip, which was prepared by pharmacists and featured medication-specific instructions. It also included designated times of the day (morning, noon, evening, and night) for dose administration (10). In contrast, our study employed a simpler MEDS-UOD packaging designed for a month with medication-specific instructions and specific morning and night dosing times. This packaging was prepared by pharmacists without requiring special skills and included the specific dates for dose administration. It offered a continuous visual record of the daily doses to be taken and facilitated the monitoring and tracking of missed doses on a monthly basis by patients, pharmacists, clinicians and caregivers. Therefore, the design of the MEDS-UOD packaging may have played a role in guiding patients to self-administer their medications punctually and gradually cultivate a habit of adherence to their prescribed treatments.

A significant improvement in medication adherence by using pill count after five months of intervention was seen in intervention group. This clearly demonstrated that the packaging intervention approach was significantly better compared to the conventional care approach. Similar finding was made in a Malaysian study where the implementation of calendar packing interventions by pharmacists for hypertensive patients found to an enhancement in medication adherence as indicated by the Medication Possession Ratio (MPR). The intervention group have higher MPR compared to the control group (p<0.05) (8). Another study highlighted the positive impact of packaging interventions using the Meds-Help approach showing statistically significant increases in MPR at 6 and 12 months among schizophrenia, schizoaffective, or bipolar patients (p<0.0001) which consisted of unit of use packaging, medication and packaging education session, refill reminders and clinician notification (10).

In another study, it was discovered that the intervention groups utilising PharmCAT and Med-eMonitor (MM) found statistically significant enhancements in medication adherence as measured by pill counts during the 9-month follow-up period in comparison to the control group (p<0.001). Nevertheless, the average treatment cost per patient per month for each of these interventions was higher in comparison to our study. This increased cost included expenses such as mileage for home visits, the cost of the monitoring

device along with web support, as well as the need for home visits for PharmCAT and refilling the monitor for MM (15). While we cannot compare the outcomes of our intervention directly because of the differences in methodology and approach, the cost of MEDS-UOD is cheaper and easier to be implemented. Thus, MEDS-UOD could be considered to improve the adherence to antipsychotics.

The difference in MARS score between CG and IG was not-statistically significant at five months of study. This outcome is similar to one study which used medication schedules and pillboxes as adherence aids in their pharmacist-assisted psychiatric clinic (14). However, when comparing the mean differences of both pill count percentage and MARS score between baseline and three months, and between baseline and five months, statistically significant improvements was observed = in the intervention group. Similar improvement was not observed in the control group. This may reflect indicate that MEDS-UOD may improve antipsychotic medication adherence. A similar result was found in a study conducted in Malaysia which uses MARS score as one of the tools to evaluate medication adherence among schizophrenia patients after giving pharmacist's intervention (Home Medication Review program). The mean MARS score at study baseline and end study was significantly improved throughout six months of study ($p<0.001$) (16).

There were several limitations in this study. The main limitation of this study was the differences in baseline characteristics between the control group and intervention group. This may potentially impact the study outcomes. Besides that, this study was only conducted in a single setting. Hence, the findings may not represent the Malaysian population of schizophrenia patients. Also, the results may not apply to elderly patients and/or those with cognitive impairment that may hinder their assessment.

The present study was conducted using pill counts method, which may lead to the Hawthorne effect. There is a possibility that patients may have discarded their pills before their visits because they worried the pharmacist might count them. Our study had no mechanism to measure this possibility. Therefore, the data collected was assumed to be accurately reported by the patient. Despite this concern, we believed that the pill counts method is an easy and cost-effective method to measure patient's medication adherence in a resource-limited setting.

Conclusion

Pharmacist intervention using Meds-UOD showed improvement in medication adherence among stable schizophrenia patients. Hence, the positive impact of introducing MEDS-UOD in pharmacist service can be considered for schizophrenia patients with compliance issues and could be implemented in other hospitals or clinics throughout Malaysia that provide psychiatric services for better patient care and aim to reduce treatment failure, rate of hospitalization and morbidity. As MEDS-UOD is still novel in our hospital setting, there is room for improvement to improve patient care and quality of life. Future studies should conduct with a larger sample size and a longer intervention period.

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Conflict of Interest Statement

This research received no grant from any funding agency in public, commercial or not-for-profit sectors. The authors declare that there is no conflict of interest.

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Liver Injury in Treatment of COVID-19 Patients: Lopinavir/Ritonavir vs Atazanavir/Ritonavir

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Abstract

Introduction: Protease inhibitors (PI) were identified as a promising treatment option for COVID-19 during the early phase of the pandemic. Incidences of elevated serum liver biochemistries have been observed in 14-53% hospitalised COVID-19 patients.

Objective: The objective of this study was to compare the proportion of liver injury between COVID-19 patients receiving lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATZ/r), to determine the time to onset to, factors associated with and clinical outcomes of grade 3-4 liver injury.

Method: A retrospective cross-sectional study was conducted among adult COVID-19 patients admitted to Sungai Buloh Hospital from 15th February to 30th April 2020, who received either LPV/r or ATZ/r as part of their treatment. Data were collected from patients' medical records in the internal Electronic Hospital Information System.

Results: This study involved 212 patients with 106 patients in each group. A statistically significant relationship between the two PIs and the severity of liver injury was found (p=<0.001). The number of patients who developed grade 3-4 liver injury in ATZ/r and LPV/r group were 27 (25.5%) and 73 (68.9% respectively. The median time to onset of grade 3-4 liver injury in ATZ/r and LPV/r group were 4 days (IQR 3) and 6 days (IQR 9) respectively. There was statistically significant associations between the type of PI used and duration of PI treatment with development of grade 3-4 liver injury in COVID-19 patients (p=0.070, Nagelkerke R^2=0.368). Among the grade 3-4 liver injury patients, 90 (90.0%) were discharged, 6 (6.0%) remained hospitalised at the end of data collection period and 4 (4.0%) deceased.

Conclusion: Liver injury was observed in COVID-19 patients receiving LPV/r or ATZ/r. More grade 3-4 liver injury were seen in the ATZ/r group.

Keywords: COVID-19, liver injury, protease inhibitor

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Introduction

In March 2020, the World Health Organization (WHO) declared the global outbreak of infectious disease caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the COVID-19 pandemic. By May 2023, COVID-19 was no longer an international public health emergency and in transition to becoming endemic (1). In the initial stages of the pandemic, when effective treatments were limited, commercially available antiretroviral agents such as lopinavir/ritonavir (LPV/r) and atazanavir were identified as one of the promising treatment options for COVID-19. In vitro studies suggest that these protease inhibitors (PI) have activity against SARS-CoV-2 via inhibition of 3-chymotrypsin-like protease enzyme (2-4). At Sungai Buloh Hospital in the state of Selangor, Malaysia, LPV/r and atazanavir/ritonavir (ATZ/r) were initially used for the treatment of COVID-19 adult patients who were in stage 3A or higher. The prescribed regimen included lopinavir 400mg/ritonavir 100mg twice daily or atazanavir 300mg/ritonavir 100mg daily for a duration of up to 10 days (5).

The use of PI-based treatments in HIV patients has been associated with hepatotoxicity, which is characterised by a significant increase in serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels, as well as unconjugated hyperbilirubinemia. The liver injury typically occurs within one to 8 weeks after initiating treatment (6, 7). The mechanisms behind drug-induced liver injury

(DILI) in these patients are not fully understood due to multiple factors (6). In hospitalised COVID-19 patients, elevated serum liver biochemistries (ALT/AST and/or total bilirubin (TB)) have been observed in 14-53% of cases, with a higher incidence in severe COVID-19 patients (8). Fan et al. reported that more than one third of COVID-19 patients in a hospital in Shanghai, China developed abnormal liver function. A high proportion of these patients had received LPV/r as COVID-19 treatment (9). Studies have indicated that liver damage is more common in patients with severe pneumonia, possibly due to inflammatory cytokines released during cytokine release syndrome (CRS) (10, 11). Inflammatory markers serve as an early alarm indicators of potential liver impairment in COVID-19 patients (12).

It remains unclear if elevated liver biochemistries are caused by the SARS-CoV-2 infection itself, CRS, ischemia/hypotension or due to DILI since some pharmacological agents used may be hepatotoxic. Hence, regular monitoring of liver biochemistries is recommended in these patients, regardless of the baseline values (8). At the time this study was conducted, PI was widely used for COVID-19 treatment. The increasing reporting of liver injury, especially in patients with severe COVID-19 stages, warrants further investigation on the possibility of DILI and other potential risk factors to liver injury. While there were many studies on PI-related liver injury among HIV patients, limited studies were done in the COVID-19 patient population. In addition, although studies have reported DILI among COVID-19 patients treated with LPV/r, no studies have compared liver injury in LPV/r and ATZ/r treated COVID-19 patients.

Therefore, this study was conducted to investigate PI related liver injury in the COVID-19 patient population and to serve as a reference for future studies. The objectives of this study were to compare the proportion of liver injury between COVID-19 patients receiving LPV/r and ATZ/r, to determine the time to onset of grade 3-4 liver injury in COVID-19 patients receiving LPV/r and ATZ/r, to determine the factors associated with development of grade 3-4 liver injury in COVID-19 patients receiving LPV/r and ATZ/r, and to describe the clinical outcomes of COVID-19 patients who developed grade 3-4 liver injury after initiation of LPV/r and ATZ/r.

Method

Study design

This retrospective cross-sectional study was conducted among adult COVID-19 patients admitted to Sungai Buloh Hospital from 15th February 2020 to 30th April 2020, receiving either LPV/r or ATZ/r as part of their treatment. Data were collected from patients' medical records in the internal Electronic Hospital Information System (eHIS). This study was registered with the National Medical Research Register (NMRR-20-900-54895). Ethical approval was obtained from the Medical Research & Ethics Committee, Ministry of Health Malaysia as well (KKM/NIHSEC/P20-1078(6)).

Study population

The inclusion criteria in this study were adults above 18 years old with laboratory-confirmed 2019-nCoV infection through real-time reverse transcription-polymerase chain reaction, receiving LPV/r or ATZ/r as part of COVID-19 treatment and are PI treatment naive. Patients who received only 1 day of treatment with LPV/r or ATZ/r without available baseline liver function test results, as well as those with missing data in the eHIS records, were excluded. Due to a change in prescribing practice during the study period, where alternative treatment options for COVID-19 were discovered, all adult patients on ATZ/r were included and matched with an equal number of patients on LPV/r. All patients were enrolled using convenience sampling. The selection of patients on LPV/r was randomized using Microsoft Excel randomization function.

Outcome measures

Primary outcome was the difference in the proportion of liver injury between COVID-19 patients receiving LPV/r and ATZ/r. The elevation of serum ALT, AST, and TB levels after the initiation of LPV/r or ATZ/r was documented and graded based on severity. Secondary outcome measures included time to onset of grade 3-4 liver injury, factors associated with development of grade 3-4 liver injury and clinical outcome of patients who developed grade 3-4 liver injury. This study focused on grade 3-4 liver injury (severe/life threatening) as these grades of liver injury were considered significant and may require intervention(s).

Definition of liver injury

Severity grading of DILI used in this study is based on the grading system developed by the Acquired Immune Deficiency Syndrome Clinical Trials Group (ACTG) as shown in Table 1. The grading system assesses the severity based on multiples of the upper limit of the normal range for ALT, AST, and TB levels. In patients with underlying liver disease, such as hepatitis B or C, the grading of liver biochemistries is adjusted to baseline values (13). In cases where there were discordant grades for ALT/AST/bilirubin, the higher grade was used for classification.

Table 1: Severity grading of drug induced liver injury

Feature	Grade 0 (Normal)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life threatening)
ALT	<1.25	1.25 – 2.5	>2.5 – 5.0	>5.0 - 10	>10
AST	<1.25	1.25 – 2.5	>2.5 – 5.0	>5.0 - 10	>10
TB	Normal	>1.0 – 1.5	>1.5 – 2.5	>2.5 - 5	>5

Normal laboratory range in Sungai Buloh Hospital:
ALT(10 - 49 U/L); AST(0 - 34 U/L); TB(>5 days-60 years: 5 - 21 umol/L, 60-90 years: 3 - 19 umol/L, >90 years: 3 - 15 umol/L)
Abbreviations: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TB = Total Bilirubin

Definition of factors associated with liver injury

A list of factors associated with liver injury in patients on PI was ascertained through review of literature: underlying hepatitis B or C, other new concomitant hepatotoxic drug use, abnormal transaminases on admission, COVID-19 disease severity, presence of CRS, age and gender.

Definition of hepatotoxic drug

A list of hepatotoxic drugs was ascertained through literature review but not limited to the following: antibiotic (penicillin/cephalosporin/azithromycin), antifungal, antituberculosis drug, paracetamol, nonsteroidal anti-inflammatory drugs, valproic acid, amiodarone, tamoxifen, methotrexate, statin, glucocorticoids and traditional medication.

Definition of COVID-19 severity staging

Following guidelines provided by the Ministry of Health Malaysia, COVID-19 severity staging is classified as follow.

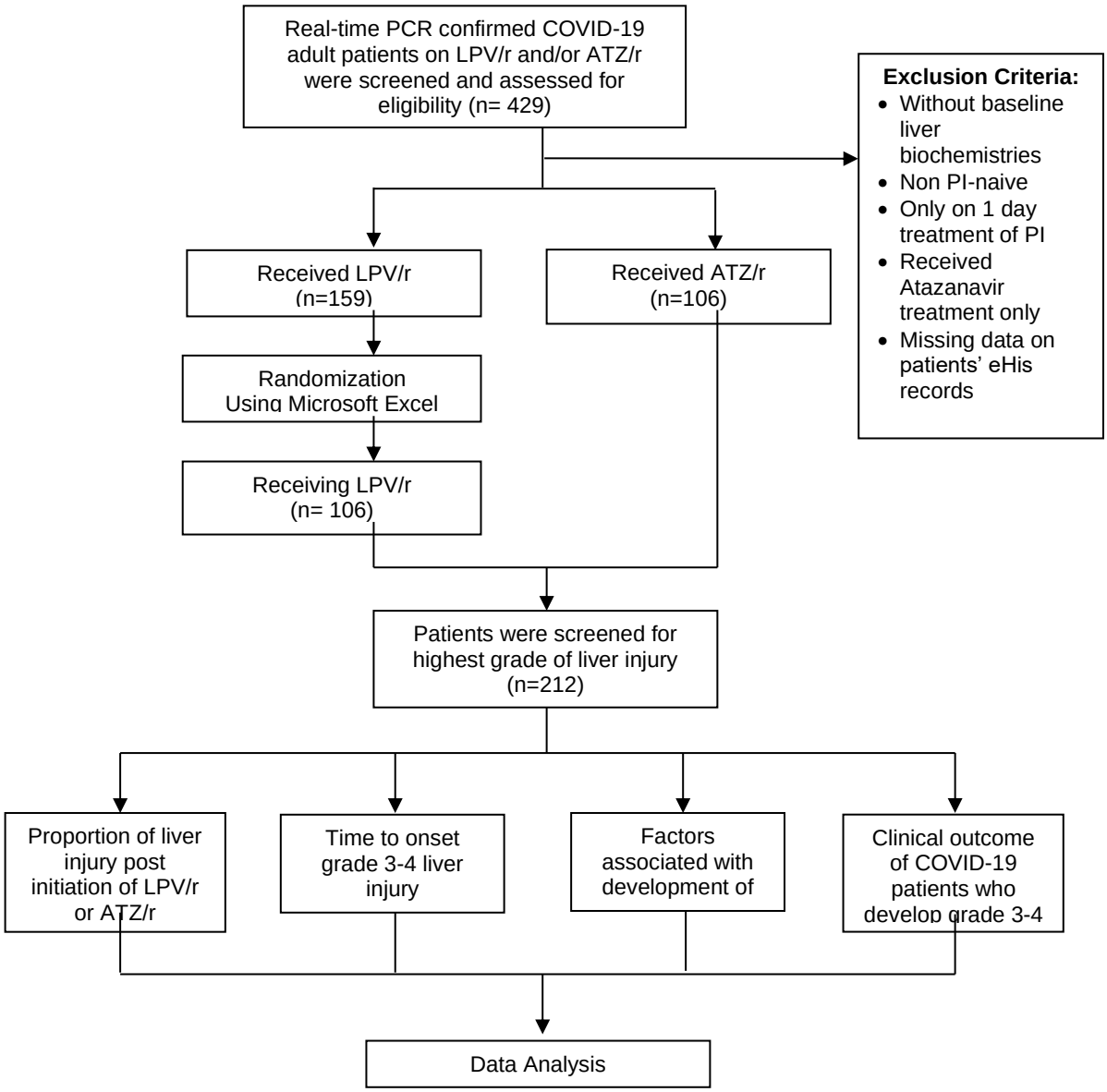
Stage 1 : Asymptomatic
Stage 2A : Symptomatic but without pneumonia without fever
Stage 2B : Symptomatic but without pneumonia with fever
Stage 3A : Pneumonia but not requiring oxygen without fever
Stage 3B : Pneumonia but not requiring oxygen with fever
Stage 4A : Pneumonia but requiring oxygen without fever
Stage 4B : Pneumonia but requiring oxygen with fever
Stage 5 : Critically ill

Statistical analysis

Categorical variables were expressed as frequency and percentages, while continuous variables were presented as medians with interquartile range (IQR), as appropriate. Comparison of categorical variables was done using Chi-square (χ^2) test. Comparison of non-parametric continuous variables was done using Mann-Whitney U test. Binary logistic regression was used to determine the factors associated with development of grade 3-4 liver injury. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 27. A two tailed P value of <0.05 was considered statistically significant.

Results

In this study, 212 patients were included, with 106 patients in each group. Study flowchart was displayed in Figure 1. The demographic and baseline characteristics were presented in Table 2. Majority of the patients in both the LPV/r and ATZ/r groups were in the age range of 51 to 70 years old. There was only one patient in the study population with underlying chronic liver disease, which was in the ATZ/r group. Among the patients, 61(57.5%) in the LPV/r group and 48(45.3%) in the ATZ/r group had abnormal liver test results upon admission. There was no statistically significant difference in demographics and baseline characteristics between LPV/r group and ATZ/r group, except for comorbidity of respiratory disease (p=0.045).



Abbreviation: PCR = Polymerase chain reaction; LPV/r = Lopinavir/Ritonavir; ATZ/r = Atazanavir/Ritonavir; PI = Protease inhibitor; eHis = Electronic Hospital Information System; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TB = Total Bilirubin

Figure 1: Study flowchart

Table 2: Demographics and baseline characteristics of study population (n=212)

Characteristics	LPV/r (n=106)	ATZ/r (n=106)	*p*-value [a]
Age (years), n (%)			
18 – 30	4 (3.8)	9 (8.5)	0.235
31 – 50	30 (28.3)	38 (35.8)	
51 – 70	67 (63.2)	54 (50.9)	
> 70	5 (4.7)	5 (4.7)	
Gender, n (%)			
Male	79 (74.5)	66 (62.3)	0.055
Female	27 (25.5)	40 (37.7)	
Ethnicity, n (%)			
Malay	81 (76.4)	82 (77.4)	0.269
Chinese	13 (12.3)	9 (8.5)	
Indian	2 (1.9)	7 (6.6)	
Others	0 (0)	1 (0.9)	
Foreigner	10 (9.4)	7 (6.6)	
Comorbidity, n (%)			
Cardio/cerebrovascular disease	48 (45.3)	57 (53.8)	0.216
Respiratory disease	11 (10.4)	5 (4.7)	0.045
Chronic kidney disease	7 (6.6)	14 (13.2)	0.108
Chronic liver disease	0 (0)	1 (0.9)	-
Endocrine	34 (32.1)	39 (36.8)	0.470
Immunodeficient/malignancy	2 (1.9)	2 (1.9)	0.651
Others	9 (8.5)	18 (17)	0.064
No known medical illness	39 (36.8)	34 (32)	0.470
COVID-19 stages, n (%)			
Mild (Stage 1-3)	46 (43.4)	50 (47.2)	0.581
Severe (Stage 4-5)	60 (56.6)	56 (52.8)	
Baseline ALT/ AST on admission, n (%)			
Normal (ALT 10 - 49 U/L; AST 0 - 34 U/L)	45 (42.5)	58 (54.7)	0.074
Abnormal (ALT > 49 U/L; AST > 34 U/L)	61 (57.5)	48 (45.3)	
Newly added concomitant hepatotoxic drugs (other than PI)	51 (48.1)	44 (41.5)	0.334

[a] p-value derived from Chi-square (X^2) analysis

Abbreviation: LPV/r = Lopinavir/Ritonavir; ATZ/r = Atazanavir/Ritonavir; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; PI = Protease inhibitor

Table 3 demonstrated the statistically significant relationship between the two PIs and severity of liver injury ($p<0.001$), except in Grade 2. Most patients who developed Grade 3 [52(49.1%)] and Grade 4 [21(19.8%)] liver injury belonged to the ATZ/r group. In this group, TB is the predominant liver biochemistry causing liver injury across all the grades. On the contrary, in the LPV/r group, many patients fall into Grade 1 liver injury [37(34.9%)]. Although in the LPV/r treatment group, the proportion of patients developing liver injury decreases as we go into more severe stages, almost all patients developed abnormal elevation in all the three liver biochemistries in Grade 4.

Table 3: Proportion of liver injury in COVID-19 patients receiving LPV/r and ATZ/r

Drug	Liver Injury Grading					$X^2(df)$	*p*-value[b]
	Normal n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)		
LPV/r (n=106)	24 (22.6)	37 (34.9)	18 (17.0)	18 (17.0)	9 (8.5)	46.939 (4)	<0.001
ATZ/r (n=106)	9 (8.5)	8 (7.5)	16 (15.1)	52 (49.1)	21 (19.8)		

[b] p-value derived from Chi-square (χ^2) analysis
Abbreviation: LPV/r = Lopinavir/Ritonavir; ATZ/r = Atazanavir/Ritonavir

There was a statistically significant difference (p<0.001) between the two groups in terms of the median peak value of TB (Table 4). The ATZ/r group had a higher median peak value [Median 68 µmol/L (IQR 46-88)] compared to LPV/r group [Median 25.7 µmol/L (IQR 17-48.3)], despite a similar baseline median for TB between the two groups. Among the 27 patients in the LPV/r group with grade 3-4 liver injury, 20(71%) of patients were continued on LPV/r while only one patient had their drug discontinued. On the other hand, 42(57.5%) out of 73 patients in the ATZ/r group who developed grade 3-4 liver injury were continued on ATZ/r; 23(31.5%) had their drug discontinued; 8(34.8%) had their drug switched to LPV/r. Majority of them in both groups were asymptomatic and their liver biochemistries returned to normal levels upon discontinuation or completion of treatment.

Table 4: Liver biochemistries of COVID-19 patients receiving LPV/r and ATZ/r

Lab Values		LPV/r (n=106) Median (IQR)	ATZ/r (n=106) Median (IQR)	*p*-value [c]
ALT (U/L)	Baseline	34 (22.0-55.3)	29.5 (16.8-48.3)	0.083
	Peak	69 (33.0-106.6)	48.5 (25.3-107.3)	
AST (U/L)	Baseline	38.5 (26.6-58.3)	30 (22-49)	0.979
	Peak	52 (35-102)	41 (28-76)	
TB (umol/L)	Baseline	9.7 (7.0-14.0)	9.8 (7.0-13.0)	<0.001
	Peak	25.7 (17.0-48.3)	68 (46.0-88.0)	

[c] p-value derived from Mann-Whitney U analysis
Abbreviation: LPV/r = Lopinavir/Ritonavir; ATZ/r = Atazanavir/Ritonavir; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; TB = Total Bilirubin

Time to onset of grade 3-4 liver injury was shorter in the ATZ/r group than in the LPV/r group [median 4 days (IQR 3 days) vs median 6 days (IQR 9 days)]. Whereas, the duration of PI treatment in the ATZ/r group were prescribed a shorter course [(median 5 days (IQR 2 days)] as compared to those in the LPV/r group [median 7 days (IQR 4 days)].

Logistic regression analysis was conducted to determine factors associated with the development of grade 3-4 liver injury among COVID-19 patients receiving LPV/r or ATZ/r as part of their treatment (Table 5). Univariate logistic regression showed that there were statistically significant associations between the type of PI used (p<0.001) and presence of CRS (p<0.001) with the development of grade 3-4 liver injury. The binary logistic regression model indicated statistically significant associations between type of PI used and duration of PI treatment (p=0.070, NagelkerkeR^2=0.368) with development of grade 3-4 liver injury. The use of ATZ/r was associated with higher odds of developing grade 3-4 liver injury (p<0.001). Underlying chronic liver disease was not included in the analysis as there was only one patient.

Table 5: Association between potential factors with development of grade 3-4 liver injury

Variable	Univariate Logistic Regression			Binary Logistic Regression		
	(b)	Crude Odds Ratio (95% CIs)	*p*-value[d]	(b)	Adjusted Odds Ratio (95% CIs)	*p*-value[d]
Age						
18-30 years old	0	1.00		0	1.00	
31-50 years old	-0.53	0.59 (0.18-1.99)	0.393	-0.61	0.55 (0.14-2.20)	0.394
51-70 years old	-0.79	0.46 (0.14-1.47)	0.189	-0.68	0.51 (0.13-2.00)	0.331
> 70 years old	0.92	2.50 (0.37-16.89)	0.347	1.43	4.16 (0.48-36.33)	0.197
Gender						
Male	0	1.00		0	1.00	
Female	0.47	1.61 (0.90-2.88)	0.111	0.40	1.49 (0.74-3.00)	0.261
Type of PI used						
Lopinavir/Ritonavir	0	1.00		0	1.00	
Atazanavir/Ritonavir	1.87	6.47 (3.55-11.79)	<0.001	2.39	10.94 (4.93-24.26)	<0.001
New concomitant hepatotoxic drug use						
No	0	1.00		0	1.00	
Yes	0.32	1.38 (0.80-2.37)	0.247	0.12	1.13 (0.52-2.47)	0.758
Presence of CRS						
No	0	1.00		0	1.00	
Yes	1.85	6.33 (2.08-19.33)	<0.001	0.92	2.51 (0.65-9.72)	0.184
COVID-19 staging						
Mild (Stage 1,2,3)	0	1.00		0	1.00	
Severe (Stage 4,5)	0.48	1.62 (0.94-2.80)	0.083	0.23	1.26 (0.58-2.75)	0.559
Abnormal ALT/AST level on admission						
No	0	1.00		0	1.00	
Yes	0.20	1.22 (0.71-2.09)	0.477	0.43	1.54 (0.74-3.19)	0.248
Duration of PI treatment, day	0.06	1.06 (0.97-1.17)	0.210	0.18	1.20 (1.05-1.37)	0.009

[d] Data analyzed using binary logistic regression (Enter method)

Constant -2.705

Hosmer and Lemeshow Test $X^2(8)=14.471$, p = 0.070; Classification table 74.1%; Area under ROC curve 80.9%

Abbreviation: PI = Protease inhibitor; CRS = Cytokine release syndrome; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase

Twenty seven (25.5%) patients in LPV/r group and 73(68.9%) patients in ATZ/r group developed grade 3-4 liver injury. Among the 27 patients who received LPV/r, 19(70.4%) were discharged, 5(18.5%) remained hospitalised at the end of data collection period and 3(11.1%) deceased. Among the 73 patients who received ATZ/r, 71(97.3%) were discharged, one (1.4%) remained hospitalised and one (1.4%) deceased. Among the discharged patients in the ATZ/r group, two were discharged with jaundice, two with elevated liver function and three with hyperbilirubinemia.

Discussion

This study was conducted to compare the proportion of liver injury between COVID-19 patients receiving LPV/r and ATZ/r as part of their COVID-19 treatment. We found that the proportion of grade 3-4 liver injury in the ATZ/r group was higher than LPV/r, which was predominantly presented as hyperbilirubinemia. Consistent with a previous study by McDonald et al. (2012), TB elevation was predominantly observed in ATZ/r patients across all grades. During this 96-week randomised controlled trial, approximately 44% of HIV patients receiving ATZ/r experienced hyperbilirubinemia (grade 3–4) (16).

Numerous studies have suggested the potential risk of hepatotoxicity in HIV patients receiving PI. The incidence of hepatotoxicity in registration trials for selected PIs were reported to be 2.2-9.5 cases in every 100 patients exposed to LPV/r,, 2-7 cases in every 100 patients exposed to atazanavir, 5.3-9.5 cases in every 100 patients exposed to ritonavir (6). During the recent COVID-19 pandemic, several studies have also reported DILI in COVID-19 patients after initiation of LPV/r treatments (9, 17, 18). These patients developed liver injury and were more likely to progress to severe disease, especially among those with abnormal liver test results which was associated with prolonged hospital stay. In our study, approximately half of the patients presented abnormal liver biochemistries upon admission. The development of grade 3-4 liver injury was observed in both ATZ/r and LPV/r group, with higher proportion in ATZ/r group.

Nonetheless, the severity of DILI could be overestimated as it was based on the elevation of liver biochemistry without clinical symptoms such as jaundice (13). Although there are studies that reported strong association of drugs used for treatment of COVID-19 with liver damage, these studies focused on the magnitude of liver enzyme elevations and not on the time to the onset of liver damage. LiverTox described that PI caused an elevation of liver enzyme within one to 12 weeks of starting therapy and the pattern of serum enzyme elevations has varied from hepatocellular to mixed to cholestatic type of liver injury (7). Wang et al. reported that ALT elevations occurred between days 4 and 17 of hospitalisation, with the mean of 7.3 days in severe cases and mean of 10.7 days in mild cases (19). In our study, grade 3-4 elevation of ALT, AST and/or TB was observed on a median of 4 days and 6 days after the initiation of ATZ/r and LPV/r respectively. Liver injury was observed even in patients on a short duration of treatment, suggesting that liver injury can occur in less than one week with PI. Considering the risk of hepatotoxicity of LPV/r, China's guidelines for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV)-infected pneumonia have recommended that the treatment with LPV/r should be less than 10 days (20).

Some of the predisposing factors that contribute to abnormal liver biochemistries in COVID- 19 patients include direct viral damage, DILI, systemic inflammatory response syndrome and cytokine storm, hypoxia-reperfusion dysfunction and reactivation of pre-existing liver disease (21-23). Two studies demonstrated that abnormal liver function was more likely to occur in severe cases and indicated that these injuries could be attributed to DILI or associated with changes in disease status (17, 19). A liver biopsy from a deceased COVID-19 patient who had elevated liver biochemistries showed moderate microvesicular steatosis, mild lobular and portal activity, indicating that the injury could be induced by the viral infection or hepatotoxic drug use (24). On the contrary, the association of COVID-19 severity, other new concomitant hepatotoxic drug use and presence of CRS with grade 3-4 liver injury were not demonstrated in this study.

Chronic obstructive pulmonary disease (COPD), among the comorbidities, was most likely to be associated with severe COVID-19, intensive care unit (ICU) admission and liver injury in COVID-19 patients (14). Liver injury associated with acute respiratory distress syndrome is proposed to be the result of paracrine action of cytokines and other pro-inflammatory mediators along with hypoxemia, oxidative stress, toxins and hypoperfusion (15). In this study, however, there were significantly more patients with comorbidity of respiratory disease in the LPV/r group but most patients who developed Grade 3 and 4 liver injury belonged to the ATZ/r group instead. More evidence is needed to determine the relationship between respiratory disease and liver injury.

Liver injury in mild cases of COVID-19 is often transient and can return to normal without requiring treatment (19, 25). In this study, majority of patients who developed grade 3-4 liver injury were discharged. Although there were 4 deaths in this study, no evidence showed that DILI was the cause of death. Fan et al. reported that LPV/r caused liver function test elevations that contributed to prolonged length of hospitalisation (9). In our study, prolonged hospitalizations for monitoring of liver function were observed in some patients, while few were discharged with abnormal liver function with appointment to monitor liver function at primary care clinics. In this study, ATZ/r-induced hyperbilirubinemia patients were mostly asymptomatic and bilirubin levels returned to normal after completion or discontinuation of treatment.

There were several limitations in this study. This study was initially designed as a pilot study. Therefore, sample size calculation was not performed. Additionally, this study was conducted in a single center in Malaysia, limiting the generalisability of the findings to other regions with varying epidemiological characteristics. There is also a possible source of bias in the patient selection method due to change in the prescribing practice during the study period. The complete history on hepatotoxic drug use, alcohol intake and traditional supplement use prior to admission were not collected. The serum liver biochemistries were also not taken at fixed intervals. There was no standardised protocol on the duration of PI treatment and recommended management upon development of liver injury in COVID-19 patients. The management of patient was based on the physician's clinical judgment. At the point of producing this report, LPV/r and ATZ/r were no longer included in the latest version of COVID-19 Treatment Guide in Adult Patients at Sungai Buloh Hospital as newer antivirals and immunomodulatory agents have been developed for the treatment of COVID-19 (26). Nonetheless, liver function monitoring is still advocated in COVID-19 patients, including those who are treated with the newer PI, nirmatrelvir/ritonavir.

Conclusion

Liver injury was observed in both groups of COVID-19 patients receiving LPV/r or ATZ/r. There is significantly more grade 3-4 liver injury seen in the ATZ/r group which presented predominantly as hyperbilirubinemia and occurred at a shorter time of onset as compared to LPV/r group. The predisposing factors that significantly contributed to liver injury include type of PI used and the duration of PI treatment. Future research could look into clinically significant liver injury in COVID-19 patients and also to develop guidelines and treatment protocol to improve hepatotoxicity management in this population.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Vancomycin Dosing Adjustment: Comparison Between Trough and AUC Method

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Abstract

Introduction: Vancomycin trough-based dosing adjustment method has been postulated to increase the incidence of vancomycin induced acute kidney injury (AKI) due to overexposure to Vancomycin. Hence the vancomycin 24 hour area under the curve to minimum inhibitory concentration (AUC24/MIC) based dosing has been reintroduced.

Objective: This study aimed to compare the occurrence of AKI, resolution of infection, average total daily dose, and the duration of treatment between the trough-based and AUC24/MIC-based methods.

Methods: This is a combination of retrospective (for trough-based) and prospective (for AUC24/MIC-based) study involving patients with normal renal function who were prescribed vancomycin for the treatment of indicated infection based on culture and sensitivity testing in Hospital Melaka. In the trough-based arm, patients' vancomycin doses were adjusted to achieve the trough level of 15-20µg/mL. Whereas in the AUC24-based arm, vancomycin doses were adjusted to achieve AUC24 target of 400-600 mg.h/liter and trough level of 10-20µg/mL.

Result: A total of 152 patients were included, with 70 patients in trough-based arm and 82 patients in AUC24/MIC-based arm. The indications of vancomycin were mainly for bone Methicillin Resistant *Staphylococcus Aureus* (MRSA) (30, 19.7%), swab MRSA (24, 15.8%), and tissue MRSA (19, 12.5%). There was no statistically significant difference in the occurrence of AKI between the AUC24/MIC-based arm (n=5, 45.5%) and trough-based arm (n=6, 54.5%) (p=0.557). There were also no statistically significant differences between the AUC24/MIC-based arm and trough-based arm in terms of number of patients with resolution of infection [64 (91.4%) vs 79 (96.3%), *p*=0.116)] average total vancomycin dose [1757.10mg (standard deviation, SD 826.85mg) vs 2125.00mg (SD 986.21mg), *p*=0.350)], and duration of treatment [13.96 days (SD 9.50 days) vs 13.39 days (SD 9.54 days), *p*=0.661)].

Conclusion: This study found no reduced incidence of AKI with AUC24/MIC-based vancomycin dosing method. The average daily dose, treatment duration, and rate of resolution of infection were the same between trough-based and AUC24-based dosing adjustment methods. Further study with large sample size is warranted.

Keywords: Vancomycin, trough-based, AUC24/MIC-based, acute kidney injury

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Introduction

Vancomycin is a glycopeptide antibiotic with bactericidal microbial activity, inhibiting the synthesis of cell wall of susceptible microorganisms (1). In Malaysia, vancomycin is widely used, either empirically or specifically, to treat infections by gram positive microorganisms, notably in cases where these infections are or at high risk instigated by MRSA (2). Since vancomycin was introduced in 1958, contributing factors such as persistent infection, prolonged vancomycin duration, treatment failure and recurrent hospitalisation have led to the emergence of vancomycin intermediate resistant *staphylococcus aureus* (VISA) and vancomycin resistant *staphylococcus aureus* (VRSA) in the past 20 years, threatening the role of vancomycin as first line treatment, and rendering health care professional to the use of second line treatment such as daptomycin, linezolid, which are of higher costs (3).

The emergence of VISA and VRSA has alerted the health care community on the importance of optimisation of vancomycin treatment (4). The ratio of AUC24/MIC is the pharmacodynamic target in assessing the adequacy of exposure and coverage by Vancomycin (5-8). However due to the requirement of multiple serum samples in this method, implicating in higher medical expenses and inconveniency, the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists in their published consensus guidelines in year 2009 has recommended MRSA infection to target trough level 15-20 mcg/mL in order to achieve AUC24 required for treatment efficacy of > 400 mg.h/liter, if the MIC was ≤ 1 mcg/mL in patient with normal renal function (9).

Vancomycin overdosing is more prevalent in trough level guided dosing compared to AUC24/MIC guided dosing. Around 60% of patients with normal renal function and therapeutic AUC of ≥400 mg.h/liter were expected to have trough concentration below 15 mcg/mL (10). Therefore, trough level orientated dosing may lead to higher risk of nephrotoxicity (9). The extent of vancomycin induced acute kidney injury and histopathologic renal damage increases with the daily exposure of vancomycin and the duration of treatment in animal model studies and human exposure-response data (11, 12).

In February 2020, the vancomycin AUC24/MIC-based protocol was implemented in Hospital Melaka for patients with normal renal function. In order to assess the impact of changing current local practice on trough level guided vancomycin dosing to AUC24/MIC guided vancomycin dosing, this research aimed to assess and compare the occurrence of AKI, clinical outcome (resolution of infection), average daily dosing, and duration of vancomycin treatment between these two methods of vancomycin dosing in our population.

Methods

This was a retrospective (for trough level guided dosing adjustment method) and prospective (for AUC24/MIC guided dosing adjustment method) observational study conducted in Hospital Melaka, Malaysia. The study was registered with the National Medical Research Registry (NMRR 20-263-53121) and approval to conduct the study was obtained from the Ministry of Health Malaysia Medical Research and Ethics Committee (MREC) and Hospital Melaka's Hospital Research Review Committee (HRRC). The study population involved patients admitted to Hospital Melaka with normal renal function (creatinine clearance ≥ 50 ml/min) who received vancomycin for the treatment of indicated infection based on culture and sensitivity testing. Patients in the critical care setting were also included. Patients were excluded from the study if the infection of concerned was meningitis or infection involved central nervous system, if vancomycin was administered for surgical prophylaxis purpose, or if the patient aged 18 years old and below.

Patients in the trough-based arm were identified retrospectively from 1st July 2019 to 31st January 2020, while patients in the AUC24/MIC-based arm were included prospectively from March 2020 to June 2021. This adjustment in the study design was prompted by the changes in the vancomycin dosing practice at Hospital Melaka, as mentioned previously. In the trough-based arm, vancomycin dosing was adjusted based on pre vancomycin administration blood sample level, which was also known as trough level in this study, to make sure that the trough level was maintained within the therapeutic range of 15-20 mcg/mL. No calculation is needed for this approach. In the AUC24/MIC-based arm, two blood samples, pre and post administration of vancomycin, were taken to calculate the AUC24/MIC using the calculation protocol as shown in Appendix 1 (9, 13). Vancomycin dosing was adjusted to maintain the AUC24/MIC within the therapeutic range of 400-600 mg.h/liter and trough level between 10 to 20 mcg/mL (10). The vancomycin serum concentrations were analysed in the Biochemistry Unit, Department of Pathology of Hospital Melaka using Siemens Atellica with particle-enhanced turbidimetric inhibition immunoassay (PETINIA) method. PETINIA is a homogeneous competitive immunoassay and the rate of absorbance is inversely proportional to the concentration of drug in the sample (14).

In Hospital Melaka, Vancomycin samplings and duration of follow up were carried out according to the Clinical Pharmacokinetics Pharmacy Handbook 2019 (15). In both methods, the trough level (pre sample) was obtained before the fourth or fifth dose of vancomycin and was collected 30 minutes or one hour before the administration of vancomycin. However, an additional post sample was required for AUC24/MIC-based method which was taken one hour after the vancomycin infusion was completed. If the vancomycin trough concentration or AUC24/MIC level were within the therapeutic targets, the dosing of vancomycin will be maintained and the monitoring process will be repeated after a week. If the trough concentration or AUC24/MIC level were not within the therapeutic targets, the dosing of vancomycin will be adjusted and the monitoring processes will be repeated after the dose adjustment. The duration of follow

up in this study was from the initiation of vancomycin until its completion or discontinuation, which ranged from 1 week to 3 months, or until patients were discharged or deceased. During the follow period, all patients were monitored routinely on creatinine, blood urea and serum electrolytes. Furthermore, daily monitoring of input/output chart, and daily review of patient's clinical response which included wound condition, vital signs, and repeated cultures for microorganism clearance were carried out.

Sample size was calculated using PS: Power and Sample Size Calculation by Vanderbilt University, and online software calculator for power analysis. All power analyses were assuming an alpha=0.05, power of 80%, m=1, dichotomous, two proportions, and independent analysis. The sample size required for this study was 206 patients. To cater for incomplete medical records, an additional 20% of samples was added to the required sample sizes. The final sample size targeted was 248 patients.

Patients in the two arms were compared for the occurrence of AKI and proportion of resolved infection using Chi-Square test. The average total daily dose, duration of treatment and the trough level collected during the treatment period between both arms were compared using Independent t-test, with significance defined as p <0.05. All statistical analyses were performed using IBM Statistical Package for Social Science (IBM SPSS) programme version 22.0 and Microsoft Excel version 2013.

Result

In total, 183 patients were evaluated for study inclusion, and 152 patients were included for analysis. The remaining were excluded due to missing of vancomycin level. There were 70 patients in the trough-guided dosing arm and 82 in the AUC24/MIC-guided dosing arm. The mean (SD) age of our study population in trough-based arm and AUC24/MIC-based arm was 50.3 (18.8) and 47.1 (16.5) years, respectively. Most of the patients in both arms were Malay and male (Table 1). The baseline median (IQR) renal function in trough-based and AUC24/MIC-based group before the vancomycin treatment was 109.5 (90.0) ml/min and 96.5 (75.0) ml/min respectively. The renal function of patients for both arms did not change much at the end of vancomycin treatment. Seven cases (10%) in trough-based group and 17 cases (20.7%) in AUC24/MIC-based group were concomitantly administered with nephrotoxic medication like amikacin, gentamicin, and amphotericin B.

Table 1: Baseline characteristics of study population (n=152)

Variables	Trough-based	AUC24-based
Age, year mean (SD)	50.3 (18.8)	47.1 (16.5)
Weight, kg median (IQR)	65.0 (26.0)	65.0 (22.0)
Gender, n (%)		
Male	42 (60.0)	55 (67.1)
Female	28 (40.0)	27 (32.9)
Race, n (%)		
Malay	51 (72.9)	52 (63.4)
Chinese	12 (17.1)	19 (23.2)
Indians	7 (10.0)	7 (8.5)
Other	0	4 (4.9)
Renal Function, ml/min, median (IQR)		
CrCL (Baseline)	109.5 (90.0)	96.5 (75.0)
CrCL (End of treatment)	105.5 (105.0)	91.5 (59.0)
Concurrent nephrotoxic drugs, n (%)	7 (10.0)	17 (20.7)
Pharmacokinetics Profile, median (IQR)		
Trough level, mcg/mL	13.9 (10.1)	10.5 (8.7)
Ke, hr-1		0.11 (0.08)
Vd, L/kg		0.75 (0.38)
AUC24/MIC		445.2 (228.2)

Abbreviation: SD = Standard deviation; IQR = Interquatile range; CrCL = Creatinine clearance (using Cockcroft-Gault); Ke = Elimination rate constant; Vd = Volume of distribution; AUC24/MIC = Area under the curve to minimum inhibitory ratio

In our study population the primary indications of vancomycin were bone MRSA (30, 19.7%), followed by swab MRSA (24, 15.8%) and tissue MRSA (19, 12.5%) (Table 2). A total of 6 (8.6%) patients from trough level guided dosing and 5 (6.1%) from AUC24/MIC-based dosing arm had observed AKI, as defined by Acute Kidney Injury Network (AKIN) (16). There was no significant difference on the occurrence of AKI between these two groups (p=0.557) (Table 3). In terms of resolution of infection, there was also no significant difference between the two groups (p=0.116) (Table 3).

Table 2: Indication of Vancomycin treatment (n=152)

Indication	Proportion, n (%)
Bone MRSA	30 (19.7)
Swab MRSA	23 (15.1)
Tissue MRSA	19 (12.5)
Blood MRSA	18 (11.8)
Pus MRSA	6 (3.9)
ETT, Sputum, Bronchoaveolar MRSA	6 (4)
Non-MRSA infection [#]	50 (33)

[#] Included corynebacterium, enterococcus, rhodococcus, staphylococcus coagulase negative, and as empirical treatment of neutropenic sepsis in patients who received chemotherapy.
Abbreviation: MRSA = Methicillin resistance staphylococcus aureus; ETT = Endotracheal tube

Table 3: The development of AKI and resolution of infection in trough-based and AUC24-based groups

Parameters	Trough-based (n=70)	AUC24-based (n=82)	Statistics[a]	
			X^2 (df)	p-value
AKI, n (%)				
Yes	6 (8.6)	5 (6.1)	0.344 (1)	0.557
No	64 (91.4)	77 (93.9)		
Infection resolved, n (%)				
Resolved	64 (91.4)	79 (96.3)	2.47 (1)	0.116
Not resolved/ death	6 (8.6)	3 (3.7)		

[a] Chi-Square test
Abbreviation: AKI = Acute Kidney Injury; SD = Standard deviation

The mean trough level of AUC24/MIC-based dosing arm (11.9mcg/mL, SD 5.8) was significantly lower than the trough-guided dosing group (15.3 mcg/mL, SD 8.2) (p=0.032). Nonetheless, there was no statistically significant difference in the mean total average vancomycin dose (p=0.35) and mean duration of treatment in both groups (p=0.661) (Table 4).

Table 4: Comparison of the measured total trough level, total daily dose and duration of treatment between trough-based and AUC24-based

Parameters	Trough-based	AUC24-based	Statistics [b]	
			t (df)	p-value
Through level, *µg/mL*, mean (SD)	15.25 (8.23)	11.93 (5.75)	2.92 (150)	0.032
Daily vancomycin dose, *mg*, mean (SD)	1757.1 (862.85)	2125.0 (986.21)	-2.43 (150)	0.350
Duration of treatment, *day*, mean (SD)	13.96 (9.50)	13.39 (9.54)	0.37 (150)	0.661

[b] Independent-*t* test
Abbreviation: SD = Standard deviation

Discussion

Nephrotoxicity is a common side effect in vancomycin-treated patients (9,17). Our analysis showed there was no significant difference in terms of AKI between AUC24/MIC-based and trough-based dosing

adjustment. Our study only managed to analyse 152 patients instead of the minimum sample size of 206 patients, hence might not be able to detect significant differences between the two arms. A systemic review and meta-analysis by Tsutsuura *et al.* in 2021 that reviewed four studies comparing between AUC24/MIC-guided and trough-guided methods concluded that the incidence of vancomycin induced nephrotoxicity (VIN) was lower with AUC24/MIC-guided method. Nevertheless, it was noted that their findings might be compromised by differences in AUC24/MIC estimation methods and therapeutic range used in these four studies (18). In another study by Philips *et al.* that recruited 2,507 patients for the trough arm and 2,471 patients for the AUC24/MIC arms across 12 hospitals, there was no differences in the incidence of VIN and duration of vancomycin therapy (19). These findings were similar to our study. The background of this study was more comparable to our research as it was conducted in hospital setting, recruited all cases of vancomycin including the empirical cases, adapted the same AUC24/MIC therapeutic range (400-600 mg.h/liter), and AKIN criteria for determination of kidney injury, as well as pharmacist-driven dosing adjustments.

The AUC24/MIC-based arm has significantly lower trough level as compared to trough-based arm while still achieving the therapeutic range. This indicated that sufficient vancomycin exposure can be achieved without having high trough level. Consequently, this approach reduces the frequency of dosing titration and therapeutic monitoring sampling to achieve high trough level as with previous trough-based dosing methods in Malaysian hospital-care. This is especially beneficial in settings with limited access to Therapeutic Drug Monitoring (TDM) services. This result was in line with the statement by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists revised concensus guideline in 2020 where AUC24/MIC can be achieved with lower trough level, hence avoiding toxicity risk from over-exposure of vancomycin (17). Our findings, however, did not show differences in the average total daily dose needed to achieve therapeutic range in both arms, hence postulating no cost-saving in term of the vancomycin usage between both arms. In contrast, study by Lee BV *et al* found that there were significant institutional cost reduction using two sample AUC24 or single sample Bayesian methods as compared to trough dosing monitoring of vancomycin (20).

Similarly, the duration of Vancomycin treatment, which averaged around 14 days, was not significantly different in both arms. This may indicate the non-inferiority of AUC24/MIC-based dosing approach as compared to trough-based dosing method. The duration of intravenous antibiotics would only be extended if there is deterioration of infected wound infection (8, 21). In terms of resolution of infection, there was also no significant difference between the two arms, although AUC24/MIC-based arm recorded slightly less patients with unresolved infections. In a study by Marko *et al.*, the treatment failure was 34 percent in which the initiation of vancomycin after the first positive culture result and the time to AUC24 target attainment longer than four days were predictive of treatment failure (22). Besides that, a study by Johnston *et al.* revealed that treatment failure was more common with trough level below 10.6 mcg/mL or AUC24 below 410 mg.h/liter (23). Hence, maintaining the therapeutic range of 400-600 mg.h/liter and trough level between 10 to 20 mcg/mL in the AUC24/MIC-based doing method would be important to ensure treatment response.

Our study had several limitations. Firstly, our sample size was relatively small and only conducted in single institution which means the result cannot be generalised. Secondly, the baseline characteristics was not controlled and compared in this study, so the outcome of this study needs to be interpreted with caution. Additionally, all patients who received vancomycin were included in this study, including critically ill or neutropenic patients. As these patients often had more complications, poor organ functions and were usually on multiple medications and concomitant nephrotoxins, which could introduce remarkable changes in their pharmacodynamics and pharmacokinetics (24).

Conclusion

Our study showed that there was no difference in the occurrence of AKI among patients treated with vancomycin using the AUC24/MIC-based and trough-based dosing adjustment methods. However, the AUC24/MIC-based method can maintain patients at lower vancomycin trough concentration without being inferior to trough-based method in term of the resolution of infection and duration of treatment. Further study could be conducted to explore the differences in vancomycin therapeutic range between MRSA and non-MRSA infections.

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Conflict of interest statement
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Appendix 1

Vancomycin: AUC-Guided Dosing Approach

Equation-based approach:

i. Based on first-order pharmacokinetic equations to estimate the AUC value
ii. Required collection of two timed steady-state vancomycin concentrations
iii. Trapezoidal equations are one of the most commonly used method

Overestimate AUC Method

A. To estimate elimination rate constant, Ke

$$Ke\ (hr^{-1}) = \frac{\ln C\ post(mcg/mL) - \ln C\ pre\ (mcg/mL)}{\tau - (t\ infusion + t\ pre + t\ post)}$$

T	:	Dosing interval (hours)
t infusion	:	Infusion time (hours)
t pre	:	Interval between pre sampling and administration time (hours)
t post	:	Interval between end of infusion and post sampling (hours)

B. To calculate expected C naught (C_0)

C naught (C_0) is an extrapolated concentration at the start of infusion

$$C_0\ (mcg/mL) = C\ post\ \times\ e^{ke\ t0}$$

C_0	:	Extrapolated concentration at the start of infusion (mcg/ml)
C_{post}	:	Measured post level (mcg/ml)
Ke	:	Elimination rate constant (hr^{-1})
t_0	:	Time between start of infusion and post sampling (hours)

C. To calculate AUC (single interval)

$$AUC\ (single\ interval) = \frac{C_0(mcg/ml) - C\ pre\ (mcg/ml)}{Ke}$$

D. To calculate total AUC

$$AUC\ (total) = AUC\ (single\ interval) \times Dosing\ frequency$$

Dosing frequency	:	If dosing frequency is 12 hourly, hence need to X 2 If dosing frequency is 8 hourly, hence need to X 3

Use of Crusade Risk Score in predicting major bleeding among acute myocardial infarction patients receiving Streptokinase

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Abstract

Introduction: Thrombolysis therapy in the management of acute myocardial infarction (AMI) significantly increases major bleeding risk. As major bleeding is associated with mortality, predicting the bleeding could improve the overall outcome of thrombolysis therapy. The use of CRUSADE risk score has not been evaluated among the Malaysian population, particularly in AMI patients who received streptokinase.
Objective: This study aimed to evaluate the association of the patient characteristics and clinical outcomes with major bleeding events and to examine the prognostic value of CRUSADE risk score in predicting major bleeding among AMI patients in Hospital Selayang.
Method: AMI patients admitted to Hospital Selayang who received streptokinase from Jan 2015 to Dec 2018 were included through universal sampling. Patients were grouped into major bleeding and non-major bleeding groups. Patients' demographic data, baseline clinical characteristics and clinical outcomes during the hospital stay were extracted from the electronic medical records. The CRUSADE risk score was calculated for all patients and tested using C statistic and receiver operating characteristics (ROC) curve.
Results: In this study, 143 AMI patients with median age of 54 years old (interquartile range (IQR) 14) were included. Three patients had major bleeding (2.1%), while 31 patients had minor bleeding (21.7%). Patients with minor bleeding and without bleeding were grouped into the non-major bleeding group (n=140, 97.1%). There was no significant differences in the demographics and baseline characteristics between the two groups. Major bleeding was associated with mortality (p=0.013) and longer duration of hospital stay (p=0.003). There was no significant prognostic value of the CRUSADE model in predicting major bleeding among AMI patients receiving Streptokinase [C=0.539; 95% Confidence Interval (CI) 0.353-0.726; p=0.816].
Conclusion: CRUSADE risk score was not an independence predictor of major bleeding in AMI patients who received streptokinase in Hospital Selayang. Future study with a larger population is needed to get more significant results.
Keywords: Acute myocardial infarction, CRUSADE risk score, thrombolysis therapy, major bleeding

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Introduction

The leading cause of morbidity and mortality worldwide and in Malaysia is coronary artery disease (1–4). According to the World Health Organization (WHO), 115.14 deaths per 100,000 population in Malaysia in 2019 were caused by coronary artery disease, which includes acute coronary syndrome, ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (2). The main goal of treatment for myocardial infarction (MI) is to reduce the size of infarct. The latest treatment modalities for MI with electrocardiographic evidence of STEMI consist of thrombolysis, percutaneous coronary intervention (PCI) and medical treatment (1, 3, 5). Reperfusion must be done early and prompt as time lost is equivalent to myocardium lost (1). Therefore, it is practicable to start thrombolysis therapy in the emergency department in order to reduce delay from first medical contact to cardiac reperfusion.

The use of streptokinase as thrombolytic agent is very common as it is effective and affordable. Mortality risk is significantly reduced by thrombolysis therapy with streptokinase, where it will restore the coronary patency (1). However, thrombolysis therapy is also associated with the increased risk of major bleeding events (4–7). In-hospital major bleeding is associated to short- and long-term mortality, stroke, MI, blood transfusion, as well as increased duration of hospital stay and cost (8). Clinical decisions should weigh between the risks of recurrent ischemia and major bleeding as both risks are associated with higher mortality rate (7).

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) score is one of the tools introduced to predict the risks of bleeding in NSTEMI patients (9, 10). This score was originally developed for NSTEMI patients, but was subsequently validated in STEMI patients (11). Previous studies reported that CRUSADE score was accurate in the prediction of major bleeding events (4). However, this score was created based on Caucasian population (5, 8), and limited studies have been performed to validate the application of CRUSADE score in the management of STEMI among the East Asian population. The score functions have not been evaluated in the Malaysian setting with different patient characteristics and treatment patterns, particularly in STEMI patients. Directly applying this prediction model may over or underestimate the bleeding risks. Therefore, this study was carried out to evaluate the association of the patient characteristics and clinical outcomes with major bleeding as well as to examine the prognostic value of CRUSADE risk score in predicting the in-hospital major bleeding among acute myocardial infarction (AMI) patients in Hospital Selayang.

Method

A single-centred retrospective study was carried out in Hospital Selayang, Selangor, Malaysia. This study was registered in the National Medical Research Register (NMRR) (ID No: NMRR-16-1817-32350) and ethics approval was granted by the Medical Research and Ethics Committee (MREC), Ministry of Health on 3rd July 2018.

All AMI patients aged above 18 years old who were admitted to Hospital Selayang and received a single dose of IV Streptokinase 1.5 million units from January 2015 to December 2018 were included in this study. Patients were excluded if they received double thrombolysis therapy (streptokinase and tenecteplase) or if they had taken oral anticoagulant prior to MI.

Sample size estimation was calculated using the population proportion formula (12). Prior data indicated that the proportion of major bleeding was 0.183 (13). If the Type I error probability and precision were 0.05 and 0.05, the targeted sample size was 167 patients.

Patients' demographic data and baseline laboratory data before streptokinase administration (i.e. hematocrit level, heart rate, systolic blood pressure, creatinine clearance-calculated using Cockcroft-Gault formula) were extracted from Hospital Selayang's electronic medical record and documented into the data collection form. All records throughout the hospital stay episode were checked and clinical outcomes such as major and minor bleeding, heart failure, cardiogenic shock and mortality were documented.

Patients were classified into two groups, namely major bleeding group and non-major bleeding group, based on the presence or absence of major bleeding. The definition of major and minor bleeding was shown in Table 1. Those with minor bleeding and no bleeding were grouped into the non-major bleeding group. CRUSADE risk score was calculated for every patient based on the baseline and clinical information collected. Table 2 showed the algorithm of CRUSADE risk score calculation (10), and Table 3 showed the risk stratification for CRUSADE risk scores.

Data were analysed using Statistical Package for Social Science (SPSS) version 21.0 and Microsoft Excel version 2013. Descriptive analysis such as frequency, percentage, median and interquartile range (IQR) were used to analyse the distribution of demographic data. Statistical tests such as Fisher's exact test (for categorical data) and Mann-Whitney test (for continuous data) were performed to compare the differences of demographics, baseline data and clinical outcomes between major bleeding and non-major bleeding groups. Meanwhile, to test the prognostic value of CRUSADE risk score, C-statistic or the area under the receiver operating characteristic (ROC) curve were used. C-statistics are commonly used in medical literature to evaluate a scoring system's capacity to distinguish between two groups of population that do and do not experience the outcome of interest. A C-statistic value of 0.5 and below suggests a very

poor model, while a value more than 0.7 suggests a good model (14). A p-value less than 0.05 was regarded as being statistically significant.

Table 1: Definition of Major and Minor Bleeding

Major Bleeding	Minor Bleeding
• Fatal bleed • ICB – confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) • Upper gastrointestinal bleed (UGIB) – confirmed by Oesophagus Duodenoscopy (OGDS) procedure • Retroperitoneal bleed • ≥ 5cm hematoma • Overt bleeding (including on imaging) with decrease Hemoglobin ≥ 5g/dl or Hematocrit ≥ 15% from baseline • Bleeding that causes substantial hemodynamic compromise that requires intervention or treatment (i.e. blood product transfusion/ Vitamin K/ Tranexamic acid).	• Gum bleeding • Spontaneous gross hematuria* • Spontaneous hematemesis* • Other bleeding not requiring treatment or causing hemodynamic compromise, resulting Hemoglobin drop by 3 – 5 g/dl or Hematocrit drop by 10 -15% (*even if hemoglobin or hematocrit drop was < 3g/dl or <10%, respectively)

Definition is based on the Thrombolysis in Myocardial Infarction (TIMI), Global Use of Strategies to Open Occluded Arteries (GUSTO) and ACUITY criteria of major/ severe bleeding(18, 20, 21)

Table 2: Algorithm to determine the CRUSADE risk score of in-hospital major bleeding

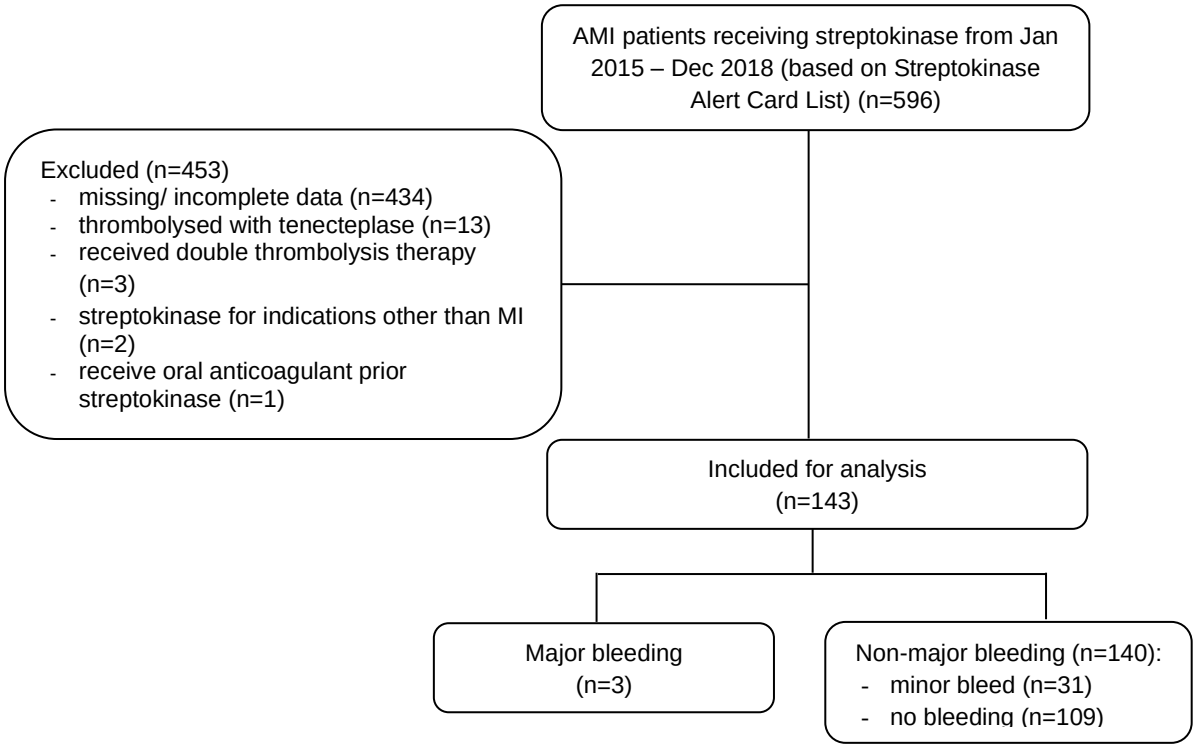
Predictor	Range	Score
Baseline Hematocrit	< 31	9
	31 – 33.9	7
	34 – 36.9	3
	37 – 39.9	2
	≥ 40	0
Creatinine Clearance	≤ 15	39
	> 15 – 30	35
	> 30 – 60	28
	> 60 – 90	17
	> 90 – 120	7
	> 120	0
Diabetes Mellitus	No	0
	Yes	6
Signs of Heart Failure	No	0
	Yes	7
Systolic Blood Pressure	≤ 90	10
	91 – 100	8
	101 – 120	5
	121 – 180	1
	181 – 200	3
	≥ 201	5
Heart Rate	≤ 70	0
	71 – 80	1
	81 – 90	3
	91 – 100	6
	101 – 110	8
	111 – 120	10
	≥ 121	11
Prior Vascular Disease	No	0
	Yes	6
Female Sex	No	0
	Yes	8

Table 3: CRUSADE Risk Score Stratification

Risk stratification	Score
Very Low	<20
Low	21 - 30
Moderate	31 - 40
High	41 - 50
Very High	>50

Results

The number of AMI patients receiving IV Streptokinase in Hospital Selayang from January 2015 to December 2017 were 596. A total of 143 patients met the inclusion criteria of this study (Figure 1). Only three patients (2.1%) were in the major bleeding group, while the remaining 140 (97.9%) were in the non-major bleeding group. There was no statistically significant difference in the demographics and baseline characteristics between the two groups (Table 4). There was also no significant difference in the CRUSADE risk score between the major bleeding and non-major bleeding group, with a median score of 23 (min, max 23, 33) and 25 (IQR 15), respectively.



Abbreviation: AMI = Acute myocardial infarction

Figure 1: Selection process of eligible patients

Table 4: Patient characteristics (n=143)

	Major Bleeding (n=3)	Non-Major Bleeding (n=140)	p- value
Age, median years (min, max / IQR)	54 (54, 73)	54 (14)	0.402[a]
Gender, n (%)			1.000[b]
Male	3 (100)	127 (90.7)	
Female	0 (0)	13 (9.3)	
Race, n (%)			0.561[b]
Malay	2 (66.7)	54 (38.6)	
Others	1 (33.3)	86 (61.4)	
Weight, median kg (min, max / IQR)	70 (60, 70)	70 (15)	0.656[a]
Smoker, n (%)	2 (66.7)	89 (64%)	1.000[b]
Co-morbidity, n (%)			
Diabetes	0 (0)	65 (46.4)	0.251[b]
Hypertension	2 (66.7)	68 (48.6)	0.614[b]
Dyslipidemia	0 (0)	26 (18.6)	1.000[b]
Prior vascular disease	0 (0)	5 (3.6)	1.000[b]
Ischemic heart disease	0 (0)	26 (18.6)	1.000[b]
Chronic kidney disease	0 (0)	10 (7.2)	1.000[b]
Heart Failure on admission, n (%)	0 (0)	32 (22.9)	1.000[b]
Baseline heart rate, median (min, max / IQR)	76 (52, 76)	86 (25)	0.132[a]
Baseline Systolic BP, median (min, max / IQR)	202 (109, 202)	138 (30)	0.260[a]
Baseline hematocrit, median (min, max / IQR)	48 (42, 48)	44 (6.8)	0.413[a]
Baseline CrCl, median ml/min (min, max / IQR)	61.7 (47.1, 61.7)	82.3 (38.9)	0.069[a]
Ejection fraction, median (min, max / IQR)	30 (30, 50)	40 (13)	0.516[a]
CRUSADE score, median (min, max / IQR)	23 (23, 33)	25 (15)	0.816[a]
Killip Class, n (%)			NA
Killip 1	2 (66.7)	85 (60.7)	
Killip 2	0 (0)	32 (22.9)	
Killip 3	0 (0)	5 (3.6)	
Killip 4	1 (33.3)	18 (12.9)	
Anticoagulant use in ward, n (%)			NA
Enoxaparin	0 (0)	15 (10.7)	
Fondaparinux	1 (33.3)	124 (88.6)	
Not on any	2 (66.7)	1 (0.7)	

[a] Mann-Whitney test, [b] Fischer exact test
Abbreviation: BP = Blood pressure; CrCl = Creatinine clearance (calculated using Cockcroft-Gault formula); IQR = Interquartile range

There were only three cases (2.1%) of major bleeding events observed in this study, while 31 patients (21.7%) had minor bleeding. Most of the bleeding cases occurred within 24-hour post streptokinase administration (20.3%), including all three cases of major bleeding. The types of bleeding identified were summarised in Table 5.

Table 5: Bleeding events observed in this study

Variables	Finding (n=143)
No bleeding, n (%)	109 (76.2)
Major Bleeding, n (%)	3 (2.1)
Intracranial bleeding	2 (1.4)
Hematoma	1 (0.7)
Minor Bleeding, n (%)	31 (21.7)
Gum bleeding	15 (10.5)
Spontaneous hematuria	6 (4.2)
Spontaneous hematemesis	3 (2.1)
Others	7 (4.9)
Bleeding onset, n (%)	
Within 24 hours	29 (20.3)
>24hours	5 (3.5)

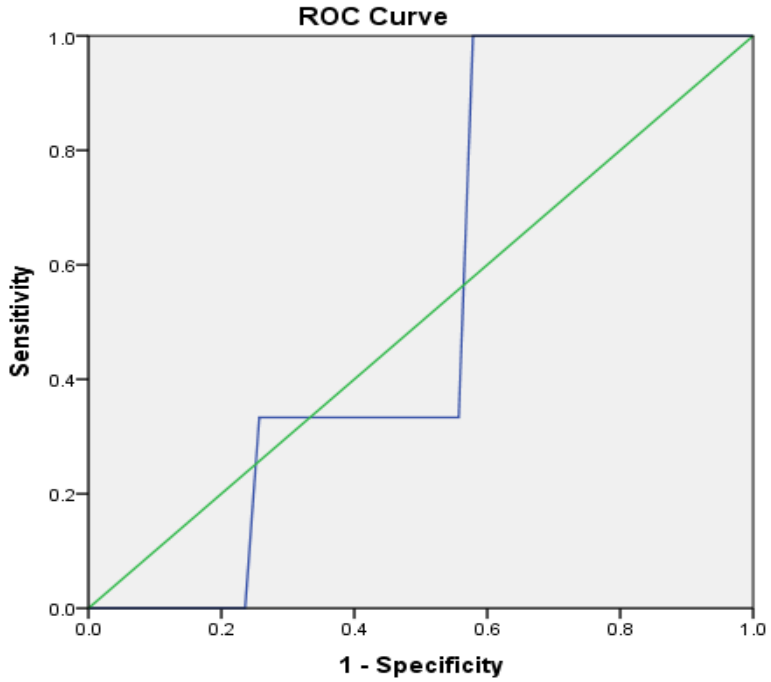
The clinical outcomes that were observed in this study were presented in Table 6. Mortality was found to be associated with major bleeding events in AMI patients receiving Streptokinase (p=0.013). Out of three patients with major bleeding, two patients (66.7%) were dead. Patients in the major bleeding group had a significantly longer duration of hospital stay as compared to non-major bleeding group (p=0.003). The median of hospital stay for major bleed group was 16 days, while non-major bleed group was only 5 days.

Table 6: Association of Clinical Outcomes During Hospital Stay with Major Bleed

	Major Bleeding (n=3)	Non-Major Bleeding (n=140)	p-value
Death, n (%)	2 (66.7)	8 (5.7)	0.013[b]
In-hospital heart failure, n (%)	0 (0)	3 (2.1)	1.000[b]
Cardiogenic shock, n (%)	1 (33.3)	17 (12.1)	0.334[b]
Length of hospital stay, median (min, max / IQR)	16 (10, 16)	5 (1)	0.003[a]

[a] Mann-Whitney test, [b] Fischer exact test
Abbreviation: IQR = Interquartile range

According to ROC curve in Figure 2, we were not able to determine a significant prognostic value of CRUSADE risk score in predicting major bleeding among AMI patients who receive Streptokinase (area under the ROC curve = 0.539; 95% CI 0.353-0.726; p = 0.816).



C=0.539; 95% CI 0.353-0.726; p=0.816
Abbreviation: ROC = Receiver operating characteristics; CI = Confidence interval

Figure 2: ROC curve for CRUSADE score with major bleeding events

Discussion

In this study, 2.1% of included patients experienced major bleeding. According to Al-Daydamony and Farag (4), the frequency of major bleeding ranged from 2% to 9% across the spectrum of acute coronary syndrome (ACS), based on the type of treatment employed, antithrombotic dosage and the invasive procedures commenced. Another study among the Netherlands population reported an incidence rate of 1% for intracranial bleeding (ICB) associated with thrombolytic therapy (15). Meanwhile, in the ISIS-2 study and ISG study, the incidences of major bleeding post Streptokinase were 0.5% and 0.9%, respectively (16).

We found that most of the bleeding events occurred within 24 hours (20.3%) after Streptokinase administration. This was comparable with a study done by McLeod et al. (17), where 15.9% of patients experienced bleeding events within 24-hour period after initiation of Streptokinase. This included those with

ICB. The first manifestation of acute bleeding observed after thrombolytic treatment was found to be ranging from three to 36 hours, with a median of 16 hours (15).

Even though there was no significant difference in the CRUSADE risk scores between patients with and without major bleeding, we found the association between major bleeding with in-hospital mortality. According to Fitchett (18), the incidence of ICB-associated thrombolysis was 0.64% to 0.94%, with an associated in-hospital mortality of almost 60% and the one-year mortality increased by five-folds. Those with major bleeding also have five times higher rates of 30-day mortality than those without major bleeding. In the GRACE registry, STEMI patients who developed major bleeding had the highest mortality rate as opposed to non-STEMI patients (22.8% vs 7%) (19).

Our study also demonstrated significantly longer hospital stay in major bleed group than those in non-major bleed group (p=0.003). Since major bleeding extended the hospital stay and increased resources consumption, it signified a source of excess expenditures (20). Minimising bleeding complications is therefore an important objective in MI management, which may favorably impact the morbidity and overall healthcare costs (18, 20).

Although several published studies demonstrated successful use of CRUSADE bleeding risk score in predicting major bleeding in various populations with ACS, our results showed the contrary. Al-Daydamony and his colleagues had studied the prognostic value of CRUSADE risk score in 240 patients with ACS, who were admitted to tertiary hospital in Egypt (4). They found that the validity of the CRUSADE risk model in predicting major bleeding was satisfactory across the ACS spectrum. The CRUSADE score ≥ 38.5 in prediction of major bleeding among STEMI patients treated with Streptokinase had the sensitivity of 70% and specificity of 85% (C=0.79) (4). CRUSADE risk score has also been evaluated in the Southeast Asia population. Jinatongthai had studied the use of CRUSADE risk score in Thai patients with ACS receiving enoxaparin (13). Their findings showed a satisfactory discriminatory capacity for the entire study population (C=0.688), unstable angina (C=0.591), NSTEMI (C=0.693) and STEMI (C=0.736). They concluded that CRUSADE score was able to predict major bleeding among Thai patients with ACS treated with enoxaparin.

On the other hand, there were also studies that reported that CRUSADE risk score had a poor predictive ability for major bleeding in certain subgroups. In a study among 544 non-ST elevation-acute coronary syndrome (NSTE-ACS) patients with age more than 80 year-old, Faustino et al. found that CRUSADE risk score had a weak discriminatory capacity for major bleeding (C=0.51) (21). Similar finding was reported by Ariza-Sole et al. where CRUSADE risk score had a lower predictive performance among ACS patients aged more than 75 year-old (C=0.63) as compared to those younger than 75 year-old (C=0.81) (22). CRUSADE risk score performance was also modest in patients who were previously on oral anticoagulants (C=0.615) and in those who did not undergo cardiac catheterization (C=0.628) (23). The discriminating power of the CRUSADE risk score in ACS patients varies significantly. This could be related to a variety of factors that make assessment of bleeding risk difficult, such as age, co-morbidities, treatment with antithrombotic agents, conservative or invasive management, and site of vascular access for angiography (24).

Since this was a retrospective study, the findings may not be sufficient to influence the current practice. However, the results obtained can be used to provide preliminary information regarding the characteristics of patients who received streptokinase and its association with major bleeding. Another limitation is that this study was conducted in a single center, hence, the results produced could not be generalised to all Malaysian populations with STEMI. The small sample size in the major bleeding group may had reduced the statistical power of this study. Also, the huge difference in sample size between the major bleeding and non-major bleeding groups could had severely impacted the data analysis, which might underestimate the true value of CRUSADE risk score.

Conclusion

This was the first study to evaluate the CRUSADE risk score in predicting major bleeding events post Streptokinase administration among AMI patients in Malaysia. We did not find any significant association between patient demographics and baseline clinical characteristics with major bleeding post streptokinase administration in AMI patients. Nonetheless, our results showed that major bleeding was associated with in-hospital mortality and length of hospital stay. This study could not demonstrate the prognostic value of

CRUSADE risk score in predicting major bleeding in AMI patients treated with streptokinase. Studies with a larger population is needed in the future to verify our findings.

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Conflict of interest statement
The authors declare that there is no conflict of interest.

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A qualitative study on barriers to smoking cessation among unsuccessful quit smoking patients at Kuala Terengganu District Health Office (PKDKT)

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Abstract

Introduction: According to the National Health and Morbidity Survey 2015, about 22.8% (4,991,458) of Malaysian population aged 15 years and above were smokers. Data from the Quit Smoking Programme in Kuala Terengganu District Health Office (PKDKT) indicated that only 31.8% of patients successfully quitted smoking from 2017 to 2019.

Objective: This study aimed to explore the barriers to smoking cessation among patients in PKDKT.

Method: Patients were selected from the registry of Quit Smoking Clinics in PKDKT. One-to-one interview session for 20-30 minutes was conducted using semi-structured questions. Purposive sampling was carried out and patients were recruited until data saturation. The interviews were audio-recorded, transcribed verbatim, coded manually and thematically analysed using constant comparison approach.

Results: A total number of 30 patients were interviewed. Six themes were emerged from this study, namely (1) personal and lifestyle factors, (2) misconception, (3) side effects of quit smoking medications, (4) recovering from acute disease, (5) withdrawal symptoms, and (6) readiness to stop smoking. Our participants claimed that it was difficult to resist temptations, and their smoking habits often relapsed due to the influence of friends who smoked in workplaces or during social activities. They stated that they switched from smoking to vaping because they had the misconception that vaping was safer compared to cigarettes. Nicotine withdrawal symptoms, such as craving, cough, constipation, sleep disturbances and weight gain, had caused patients to resume smoking. Also, the side effects of medications for quit smoking such as nausea, headache and sleep difficulties could discourage the patients from continuing their quitting efforts.

Conclusion: Six barrier themes that were related to the failure in quit smoking attempts were identified. Strategies can be designed and implemented to overcome the barriers and to improve the success rate of Quit Smoking Programme.

Keywords: Smoking cessation, barrier, qualitative, patient

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Introduction

According to the data from World Health Organization in 2021, tobacco had killed more than eight million people every year with more than seven million of deaths being the result of direct tobacco use while around 1.2 million were the result of non-smokers being exposed to second-hand smoke. The burden of tobacco-related illness and death was heaviest in low- and middle-income countries which represent 80% of the 1.3 billion tobacco users worldwide (1).

In 2015, over 1.1 billion people smoked tobacco worldwide. According to the National Health and Morbidity Survey 2015, approximately 22.8% (4,991,458) of Malaysian population aged 15 years and above were smokers. Among those who have tried to quit smoking, the abstinence rate at six months was only 3%–5% among those who self-quit and 19%–33% among those who opted for pharmacotherapy (2, 3).

The Kuala Terengganu District Health Office (PKDKT) in the state of Terengganu, Malaysia implemented the Quit Smoking Programme in its health clinics. Based on the report from the programme in 2017 and 2018, only 24.3% and 50.6% successfully quitted smoking after being enrolled in the programme. In one of the PKDKT's clinics, Manir Health Clinic, out of eleven registered patients, none of them succeeded to quit smoking and 52.2% succeeded in 2018. Overall, the success rate on smoking cessation in PKDKT was only 30% which was considered low. Although the trend of success rate was increasing, it was still far from our goal. Hence, this study was conducted to explore barriers to smoking cessation among smokers. It was hoped that this information can help in establishing strategies to increase the success rate of the Quite Smoking Programme.

Method

A qualitative study was conducted using grounded theory method to understand the barriers to smoking cessation among unsuccessful quit smoking patients who already joined Smoking Cessation Clinic in PKDKT. This study was conducted in Hiliran and Manir Health Clinics, Kuala Terengganu district, Malaysia from 1 November 2020 till 31 August 2021. Participants were recruited using purposive sampling. Consented smokers who failed to quit after attending the Quit Smoking Programme for six months at Hiliran and Manir Health Clinics were included in this study.

Eligible participants were contacted via phone to explain the purpose of the study and they were invited to meet the investigators at selected health clinic for an interview session. Sample size was determined on the basis of theoretical saturation. Informed consent was obtained from the participants before the interview session.

One to one in-depth interviews were conducted using a semi structured interview guide. Questions in the guide was developed to probe into the experiences of quitting smoking and resuming smoking after attempting smoking cessation. The interview guide was translated to Malay language by an English teacher from a higher education institution who has good command of Malay. The translated interview guide was pre-tested on three participants who had previous experience in smoking cessation programme. Adjustment was done to increase the understanding, engagement, depth and scope of the interviews. The participants involved in the pre-test study were not included in the study data set. The interviews were conducted by three investigators (WN, NL, NS) in Malay or local dialect according to participants' preferences. All investigators discussed before the interview process to ensure the consistency in the questions given. The duration of interviews took between 20 to 30 minutes. Data collection was terminated when the saturation point was achieved.

The interviews were audio-recorded using digital recorder and transcribed verbatim. The transcripts were translated to English by the interviewers. The process of data analysis started with line-by-line open coding to ensure that the analysis was comprehensive. Coding was carried out independently by WN and NL to reduce bias. Constant comparison approach was used to link the fragmented code and developed the theme.

The study conducted was in compliance with the national and international conditions and guidelines stipulated in the Declaration of Helsinki, World Medical Association (WMA). Approval from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia was obtained and and the study was registered under the National Medical Research Registry (NMRR-20-2836-55485 86).

Results

Of 52 participants who failed to quit smoking after six months programme in Health Clinics, 15 refused to participate in the study and five was un-contactable. In total, 30 participants were included in this study. All of them were male, with the mean age of 42.7 (standard deviation, (SD) 10.33) years old. Most of them had secondary education and above and had been smoking for more than 15 years (Table 1).

Table 1: Demographic of the participants (n: 30)

Demographic characteristic	n (%) / Mean ± SD
Age, mean ± SD	42.7 ±10.33
Gender	
Male	30 (100.0)
Education	
Primary	4 (13.3)
Secondary	15 (50.0)
Tertiary	11 (36.7)
Years of smoking, mean ±SD	20.2 ± 8.61
<10 years	2 (6.7)
11-15 years	7 (23.3)
>15 years	21 (70.0)

Abbreviation: SD = Standard Deviation

Six themes were generated from this study, namely (1) personal and lifestyle factors, (2) misconceptions, (3) side effects of quit smoking medications, (4) recovering from acute disease, (5) withdrawal symptoms, and (6) readiness to stop smoking.

Theme 1: Personal and life style factors

A majority of participants stated that they were unable to resist temptations when they tried to quit smoking. Their smoking habit relapsed due to the influence of friends who smoked in workplaces or during social activities.

> *"If I mingled with my friends, I felt that I must smoke and I don't know why".* (Participant 1)
> *"I always smoke if I mingled with my friends who are still smoking".* (Participant 5)
> *"When my relatives offer me a cigarette… I had to accept even only for one cigarette to avoid negative impression … e.g. arrogance."* (Participant 28)

Participants also stated that quit smoking might impaired their alertness.

> *"I'm not successful in quitting smoking because without cigarette I feel sleepy during driving and reduce my focus on work. I felt very fresh and energetic if I kept on smoking".* (Participant 4)
> *"… Lorry driver like me needs to smoke to stay alert. If I'm not smoking, I feel sleepy and tired. I manage to stop smoking for only two days before I start smoked again".* (Participant 17)

Some participants stated that their failure was related to stress, boredom, and impulsive decision.

> *"I will smoke if I felt stress."* (Participant 5)
> *"I can stop smoking for four months before. But I felt so bored…all my friends still smoking… I started smoking again without a concrete reason. Just because I felt bored and just for fun."* (Participant 15)

Theme 2: Misconception

Participants also expressed their misconceptions. They perceived that vaping was better than smoking with less side effects.

> *"When I joined the quit smoking programme, I got the recognition since I was able to quit smoking…after that I change to vape because vaping for me is more acceptable and better than smoking"* (Participant 6)
> *"I felt better nowadays since I quit smoking. But I do vape since vaping had fewer side effects to health".* (Participant 13)

Some participants thought that they will succeed in quit smoking after taking smoking cessation medications for a short term.

> *"I took Champix for 14 days but I'm not feeling better. Still had the craving to smoke… No effect on me".* (Participant 23).

"I thought after I started the smoking cessation medication, the craving to smoke will disappear but nothing happened to me. I still felt the crave to smoke…. Medication had not given any effect to me". (Participant 29)

Theme 3: Withdrawal symptoms

Most of the participants also said that their failure was due to withdrawal symptoms of nicotine. They experienced increased body weight, craving, tachycardia, fatigue and difficulty to maintain focus. Increase in body weight had severe impact especially on young participants.

"My weight kept on increasing after I stop smoking. As a young man, I cannot accept that. So, I started smoking again". (Participant 9).

"No smoke made my life miserable… always felt angry, cannot focus in work and my body weight started to increase. Body weight issue made me so stress. Then I started smoking again" (Participant 10).

"I stop for two to three months… but my weight increased more and more… and I was having palpitation. I felt so scared. Then I started smoking again with my friends". (Participant 11).

Theme 4: Recovering from acute disease

Participants were able to control themselves by not smoking during disease such as acute asthma exacerbation or heart attack but they resumed smoking upon recovery.

"I had asthma but I'm not quitting smoking. I just cannot quit. When I'm having an asthma attack and hospitalised, I quit smoking for a while as the doctor advices to do so, but then when I was discharged from hospital, I started smoking again since I felt better". (Participant 17)

"I joined quit smoking programme since I saw a lot of other patients joined that clinic. I myself had no plan and determination to quit smoking. I only quit smoking if I am sick, but then I started smoking again". (Participant 5)

"I had asthma, I only quit smoking if I'm having an asthma attack. If not, I smoke". (Participant 9)

"I successfully quit smoking for six years in 2000. That's the longest achievement. At that time, I was having bad cough and asthma attack. I was hospitalised for a long time. If I was still smoking at that time, I might be dead. However, after discharged from hospital, I started smoking again. I just cannot quit since I felt healthy". (Participant 2)

Theme 5: Side effects of medication

Medication used in quit smoking programme include varenicline tablet (Champix), nicotine gum and nicotine patch. Common side effects reported by the manufacturer include nausea, headache, constipation and insomnia. Some of the participants cannot tolerate the side effects of medication which made them resumed smoking.

"I used Champix for three to four months but I experienced the side effect of dizziness. After that, I started smoking again. So difficult to quit smoking". (Participant 18)

"When I started Champix, I had nausea and dizziness. As time went by, it felt better. Smoke felt bitter to me. So, I quitted for two to three months. But I cannot tolerate the side effects of palpitation. I felt so scared. I'm afraid my blood pressure will increase and I will get hypertension. Then I started smoking again especially if I mingled with the other smokers". (Participant 11)

"When I started Champix, I felt nausea and dizziness a little bit. Then the side effects became stronger. Medication … from twice times daily, I took once daily then I stopped taking that medication". (Participant 24)

"I usually took Nicotine Gum after Isya' …. after dinner. So if I chew the gum, I cannot sleep at night. If not, I can sleep as usual". (Participant 14)

Theme 6: Readiness to quit smoking

Some participants were not voluntarily involved in the Quit Smoking Programme. They were forced by their family members.

"I joined the Quit Smoking Programme since my wife registered for me. I had no interest and determination to quit smoking. I only quitted smoking for two to three months". (Participant 25).

"I had the intention but no determination to quit smoking. I only quitted smoking during the fasting month. Then I started to smoke again". (Participant 19)
"I cannot give the commitment to follow the Quit Smoking Programme schedule. That's why I'm not interested to join this programme". (Participant 26).

Discussion

This study found six barrier themes that were related to the failure in quit smoking attempts. One of the major barriers identified in this study was personal factors and social lifestyles. Our participants quoted that they were influenced by their friends and relatives who are smokers, and they failed to resist when their friends offered them cigarettes when they were hanging out together. Likewise, Sharma et al. found that the main reason of failure to quit smoking was the influence of friends. Smokers often have the perception that smoking will increase their circle of friends, increase enjoyment and for stress relaxation (4). Similarly, according to Chean et al., the personal and lifestyle factors encompassed the presence of other smokers, easy access to cigarettes, impaired self-control and boredom. The authors concluded that smoking cessation needs will power and a strong mind set (5).

Some of our participants claimed that they resumed smoking when they were stress, bored, and even restarted smoking without any reason. Previous study reported that smokers had more pleasure when exhaling the smoke and they saw smoking as a source of pleasure rather than addiction (4). Chellappa et al. also reported that most of the smokers were aware of the harms of smoking but still fail to quit because they enjoyed smoking, and not because of addiction. Satisfaction they get from the taste of smoke was beyond the effects of nicotine replacement therapy (6). In relation, Kim et al. reported stress, grief and loss as the primary obstacles in quitting smoking and avoiding relapse. High level of stress can be due to health concerns, excessive work, inequity in the workplace, and family issues. Fears also caused some participants from embarking on a quit attempt and being successful in quit smoking. The fear of failure, fear of feeling sick during the quit attempt, fear of weight gain, and fear of losing an effective coping mechanism affected the quit smoking outcome. There were also pressure to smoke in social situations where a high proportion of smokers are present (7).

Our participants claimed that they switch from smoking to vaping because they believed that vaping was safer compared to cigarettes. This was a common misunderstanding among the public and was often used as a justification by smokers or previously successful quitters to start vaping (8). Healthcare professionals, government, non-government organisations, media and other parties should step up the efforts to educate the public about the danger and side effects of vaping. On the other hand, some of our participants misbelieved that they can automatically stop smoking after using the varenicline starter pack for 14 days. They were disappointed when they still felt the tobacco craving after the first two-week treatment. This disappointment caused them to give up on the treatment. To prevent this issue, clinicians and pharmacists can allocate more time to counsel the patients before initiating treatment with varenicline to make sure that patients fully understand the regimen and set reasonable expectations.

Our study found that the side effects of medication for quit smoking such as nausea, headache and sleep difficulties could discourage the patients from continuing their quitting efforts. Participants with night dose of varenicline and/or nicotine gum complaint of having sleep difficulties, and they claimed that they can sleep comfortably after stopping the medication. According to Ashare et al., sleep disturbance might be one important side effect of nicotine replacement therapy. However, sleep disturbance on smoking cessation was complicated by the fact that nicotine withdrawal also produced sleep disturbances (9). Besides sleep disturbances, other common withdrawal symptoms were craving, cough, constipation and weight gain. Although patients were usually counselled about the withdrawal symptoms before beginning the quit smoking attempt, these symptoms could be disturbing and may cause patients to resume smoking to eliminate the symptoms. Bush et al. reported that while post-cessation weight gain was experienced by majority of people who quit smoking, the degree of weight gains varied considerably. Smokers may try to overcome nicotine withdrawal by substituting smoking with eating, and this could cause increased calorie intake. In addition, post-cessation weight gain may also be the consequence of low satiety, emotional eating, calorie misperception, and short sleep (10). Nicotine replacement therapy was effective in delaying post-cessation weight gain. Intermittent very-low-calorie diet with nicotine replacement therapy showed improved success rate of smoking cessation while prevented weight gain (10).

Smoking is a major risk factor for cardiovascular, respiratory, cancer and many other diseases. Patients were usually advised to quit smoking to reduce their risk factors. However, some of our study participants with chronic or acute disease said that they resumed smoking after their acute events or exacerbations were resolved. They were able to stop smoking for a short period, but continue to smoke after they felt better and healthier. In a study involving patients treated for tuberculosis who received smoking-cessation interventions in Indonesia, Mark et al. found that up to 84% of patients who quit smoking were able to maintain their abstinence for up to six months after the intervention, although the patients were not followed up to determine the long term outcomes of the intervention (11).

Some of our participants stated that they joined the Quit Smoking Programme involuntarily. Although they attended clinic appointments, they failed to quit because they were not ready. Willingness and readiness of smokers to quit smoking played a very important role for their success (12). In a study by Kim et al., some smokers experienced the pressure to quit from non-smokers, which made them felt like they were getting 'picked on' (7). This experience made some of them wanted to smoke more. Smokers' readiness to quit was divided into five stages, which include precontemplation (not thinking about quitting), contemplation (thinking about quitting but not ready to quit), preparation (getting ready to quit), action (quitting) and maintenance (remaining a non-smoker). Patients should identify which stage they were currently in (13). Motivational interviews by clinicians to explore patient's ambiguity to smoking cessation was important. Discussions between the patients and clinicians in determining the treatment plan and social support would be helpful. In addition, patients should have frequent contact with the healthcare team for support and solutions in managing any difficulties.

The main limitation of this study was the possibility of recall bias since the nature of this study was based on self-reporting. Furthermore, transferability of the data which means these findings cannot be extended to wider populations with the same degree of certainty that quantitative analyses can. Finally, this study used a manual method for analysis and no software were used for the data sorting and transcribing.

Conclusion

This study found six barrier themes that were related to the failure in quit smoking attempts, which were personal and lifestyle factors, misconceptions, side effects of quit smoking medications, recovering from acute disease, withdrawal symptoms, and readiness to stop smoking. We hope that the findings from this study could help the Quit Smoking Programme team members and healthcare providers to establish strategies to overcome the barriers of quit smoking and increase the success rate. Healthcare practitioners needed to provide sufficient knowledge to patient in order to improve their confidence, to acknowledge withdrawal symptoms and to focus more on the end results during the smoking cessation process.

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Conflict of interest statement

No external funding was received and the authors declared that there was no conflict of interest.

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