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SABAH LOCAL FRUITS ASSOCIATED WITH NUMBER OF INR OUT OF RANGE IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION RECEIVING WARFARIN THERAPY: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Drug-fruits interaction affects optimal anticoagulation, but little is known about this topic due to limited researches. This study aims to investigate the association between Sabah local fruits consumption among non-valvular atrial fibrillation patients receiving warfarin therapy and number of international normalised ratio (INR) out of range. A retrospective observational study was conducted on patients attending clinic from April 2016 to April 2017. Predictor variables measured were number of clinic visits with local fruits consumption, types of local fruits consumed and number of local fruits consumed within 1 week before clinic visit. Negative Binomial Regression Model was used to determine predictor associated with number of INR out of range. A total of 109 atrial fibrillation (AF) patients were evaluated, with an average age of 65.33 ± 9.59 years and predominantly male (n = 66, 60.5%). A total of 946 of the 1,274 clinic visits recorded local fruits consumption during past one week. Increase in number of clinic visits with local fruits consumption was associated with 8% higher number of INR out of range, and it was significantly higher among patients who consumed Durian (incidence rate ratio [IRR] = 1.152, 95% confidence interval (CI) 1.004–1.322, p = 0.043), Tarap (IRR = 1.237, 95% CI 1.051–1.456, p = 0.010), Pineapple (IRR = 1.115, 95% CI 1.032–1.204, p = 0.005), Cempedak (IRR = 1.278, 95% CI 1.025–1.594, p = 0.029), Banana (IRR = 1.056, 95% CI 1.029–1.085, p < 0.001), and Papaya (IRR = 1.048, 95% CI 1.016–1.081, p = 0.002). Besides, taking either one or more types of local fruits significantly increased the number of INR out of range. In the final regression model, only number of clinic visits with local fruits consumption was retained (IRR = 1.08, 95% CI 1.05–1.10, p < 0.001). Local fruits consumption significantly affects quality of anticoagulation with warfarin; it should be considered when assessing possible cause of deranged INR.

Keywords: Warfarin, Sabah, fruits, interaction, association

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INTRODUCTION

Warfarin, the oral anticoagulant has been the gold standard for prevention and treatment of thromboembolic events (Holbrook *et al.* 2005). Despite the emergence of the non-vitamin K antagonist (NOACs) with increasing evidence of safety and efficacy, as well as the benefit of lesser interaction and predictable pharmacokinetics, warfarin is still widely prescribed, including conditions where use of NOACs is contraindicated, such as mechanical valve replacement, severe mitral valve stenosis and pregnancy (Steffel *et al*. 2021)

The safety and effectiveness of warfarin rely on maintaining consistent international normalised ratio (INR) within the target range (Norwood *et al.* 2014), and also ensuring adequate time in therapeutic range (TTR >70%) as per European Guideline suggestion. Quality of warfarin management is correlated with hemorrhagic and thromboembolic rates (Hindricks *et al.* 2021; Zulkifly *et al.* 2018). Unfortunately, attaining optimal anticoagulation with this agent is clinically challenging in view of its narrow therapeutic index and extensive interaction potential (Nutescu *et al.* 2006). Numerous factors have been shown to affect anticoagulation effect of warfarin such as drug-drug interaction, drug-food interaction, disease states, alcohol consumption and the patient's lifestyle (Holbrook *et al.* 2005). Poor anticoagulation control will lead to increased risk of bleeding or thromboembolic complications (Oake *et al.* 2008).

Drug-drug interactions that exist with warfarin are well documented. In contrast, there are only a limited number of studies on the interaction between warfarin and fruits. An article published in 2014 has reviewed a total of 15 case reports and 7 controlled clinical trials on the effects of warfarin-fruit interaction. Cases with possible warfarin-fruit interactions resulted in deranged INR, as well as bleeding episodes such as hematuria, hemoptysis, hematochezia, hematoma requiring hospitalisation and even fatal gastrointestinal and pericardial hemorrhage have been reported. In view of this, the author had suggested for more randomised controlled study to better ascertain the potential interactions. (Norwood *et al.* 2014).

From our clinical observation, increased consumption of Sabah local fruits among patients taking warfarin may be associated with a higher trend of INR out of range. However, studies on the aforementioned interaction are scarce and the effects are hence not fully understood. Through this study, we aim to determine the association between local fruit consumption and number of INR out of range in non-valvular atrial fibrillation (NVAF) patients. Raising awareness of this topic is crucial for clinicians and pharmacists managing warfarin anticoagulation clinic, to improve the quality of patient care and optimise patient outcome through warfarin dose adjustment and patient education.

METHODS

Study Design

This retrospective observational study was conducted at Queen Elizabeth Hospital, Kota Kinabalu, Sabah, Malaysia, where patients' warfarin treatments were managed by pharmacist during Medication Therapy Adherence Clinic (MTAC). Throughout the study period, patients were evaluated on their local fruits consumptions during clinic reviews, with INR monitoring done. All included patients were followed up for a total duration of one year. No informed consent was required because this was an retrospective observational study. Relevant information was obtained from patient's case notes. All data were collected using prepared data collection form.

Subjects

All adult patients (> 18 years old) under MTAC Warfarin during our study period on 1 April 2016–1 April 2017 were screened and included.

The inclusion criteria for this study were uninterrupted warfarin treatment for at least six months, and history of at least five clinic visits for patients newly started with warfarin. Patients with INR testing conducted using Point-of-Care System (POC), complete loss to follow up and pregnant patients were excluded from this study.

All patients followed up during MTAC Warfarin serve as sampling frame in this study (n = 192). Convenience sampling was adopted. Participants were screened and recruited in the study if inclusion/exclusion criteria were fulfilled until sample size was achieved.

Fruits Consumption Evaluation

Fruits consumption evaluation was performed using a prepared pictorial chart to aid patients in identifying types of local fruits that had been consumed, including banana, papaya, watermelon, mango, pineapple, *langsat*, rambutan, guava, durian, *tarap*, *cempedak*, orange, *duku*, mangosteen and *bambangan*. Fruits consumed for the past one week before clinic reviews were of our primary interest as it would potentially affect INR values.

Data Collection for Parameter of Interest

All data in this study was obtained retrospectively from patients' case note using a data collection form. These included baseline demographics such as age, gender, weight, height, co-morbidity, race, occupation, marital status, education level, smoking status, alcohol status, warfarin indication and target INR. Subsequently, fruits consumption related variables were assessed such as types and number of fruits consumed for the past one week.

Research Outcomes

Our primary outcome was the number of INR out of range associated with local fruits consumption within the past one week of clinic visits. We aim to determine how local fruits consumption, in general, may affect patients' INR, by investigating if increased number of clinic visits with reported local fruits consumption is associated with higher number of INR out of range.

INR out of range is defined as INR not within target range (1.8–3.2). Instead of the therapeutic range 2.0–3.0, we used an expanded INR of therapeutic range INR ± 0.2, as such variation of INR from therapeutic range is considered clinically insignificant, hence no dosage adjustment is required (Saokaew *et al.* 2012). This is also in accordance with Malaysian Ministry of Health Warfarin MTAC protocol (1st Edition), which was the latest protocol available at the time of this study.

Our secondary outcomes were individual factors that may affect the number of INR out of range. We would like to investigate if number of INR out of range can be related to factors such as the specific type of fruits consumed; and the number of types of fruits (one type or more than one type) consumed in the past one week before clinic visits.

Sample Size

Patient on warfarin treatment serve as the analysis unit in this study. To estimate the number of INR out of range among patients treated with warfarin, the required sample size was 108 (standard deviation of number of INR out of range was estimated as 3.1) for the margin of error or absolute precision of 0.5 in estimating the mean number of INR out of range with 95% confidence and considering a potential loss/attrition of 20%. This sample size is calculated using sample size calculator for estimating mean with finite population correction (total patient under MTAC Warfarin reviewed was 192) (Naing *et al.* 2006).

Statistical Analysis

All data obtained was initially recorded in Microsoft Excel Spreadsheet for compilation. Subsequently, further data analysis was conducted using STATA/SE 12.0 (StataCorp, College Station, TX, USA). Prior to any data analysis, the sampling distribution was assessed. The data was evaluated for any significant deviation from normality using a frequency distribution (histogram) and a Q-Q plot (quantile-quantile plot). The frequency distribution plots the observed values against their frequency, provides both a visual judgment about whether the distribution is bell shaped. On a Q-Q plot, normally distributed data appears as roughly a straight line. To further confirm that the continuous variables were normally distributed, normality test using Shapiro-wilks was adopted (n > 100). A *p*-value of > 0.05 showed that there was enough evidence to accept null hypothesis that the variables were normally distributed. For normally distributed continuous variables, the data were presented in mean and standard deviation (SD). If the data was not normally distributed, it would be reported as median and interquartile range (IQR). For categorical data, result was presented as frequency and percentage. We adopted descriptive statistical analysis to present baseline characteristics for all our patients. To identify the potential independent variables that were associated with dependent variables of number of INR out of range, negative binomial regression (NBR) was adopted. This regression method was used since the dependent variable (number of INR out of range) was a discreet count data, the variance (13.1) of the number of INR out of range is higher than its mean value (5.3), the distribution of the number of INR out of range is rightly skewed and there was a high lower values of number of INR out of range as compare to higher values. This model assessed the interrelationship of independent variable that may influence the effect of outcomes while adjusting for the impact of potential confounding variables. Confounding variables were baseline characteristics observed during analysis. Incidence rate ratio (IRR) was used to assess the strength of relationship between the independent variables and dependent variable. Initial simple NBR was conducted to screen all potential predictors and only independent variables with *p*-value less than 0.05 and biological plausibility were considered for subsequent multivariate analysis. For a robust build-up of the model, forward stepwise elimination was adopted to eliminate variables that were not associated with outcomes. Final model was obtained when NBR assumption was met. All statistical analyses were two tailed and considered as statistically significant at *p*-value less than 0.05.

Medical Research Ethics Approval

Ethical approval was obtained from Clinical Research Centre (CRC) and Malaysian Research Ethics Committee (MREC). Expedited review was obtained because no human intervention was involved and no informed consent was needed. Our research ID is NMRR-17-678-35502 (IIR).

RESULTS

Basic Demographic Data

Out of all 192 MTAC Warfarin patients screened, we included a total of 109 subjects in this study (150 subjects met the inclusion criteria; 41 of them whose warfarin was not indicated for NVAF were excluded). Their target INR was 1.8–3.2. Majority of these patients were male (n = 66, 60.55%), with a mean age of 65.33 ± 9.59. Ninety-five patients (87.16%) were non-alcoholic drinker and 67 patients (61.47%) were non-smoker, as shown in Table 1. Most of the subjects were non-KDM (Kadazan/ Dusun/ Murut ethinic), which include Malay, Chinese, Bajau and others (n = 75, 68.81%).

Table 1: Baseline demographics for NVAF patients (n = 109).

Variable	Value (%)
Age (Mean ± SD)	65.33 ± 9.59
Gender	
Male	66 (60.55)
Female	43 (39.45)
Race	
Non-KDM	75 (68.81)
KDM	34 (31.19)
Education	
No	22 (20.18)
Yes	87 (79.82)
Occupation	
Unemployed	27 (24.77)
Employed	82 (75.23)
Marital Status	
Married	103 (94.50)
Single	6 (5.50)
Place of Resident	
Family	101 (92.66)
Nursing Home	8 (7.34)
Smoking Status	
No	67 (61.47)
Yes	42 (38.53)
Alcohol Status	
No	95 (87.16)
Yes	14 (12.84)
Number of co-morbidity (median, IQR)	3 (2,4)

Note: KDM = Kadazan Dusun Murut

There was a total of 1,274 clinic visits involving the included subjects, in which 946 of the visits recorded consumption of local fruits for the past one week. Overall mean number of INR out of range (not achieving target INR 1.8–3.2) was 5.25 ± 3.61 per patient. Commonly, our patients experienced four number of INR out of range throughout the study period (n = 17, 15.5%).

Types of Local Fruits Consumed

Figure 1 shows the types of local fruits consumed. Those most frequently consumed include banana, papaya and watermelon. On average, patients took 1–3 types of local fruits at one time.

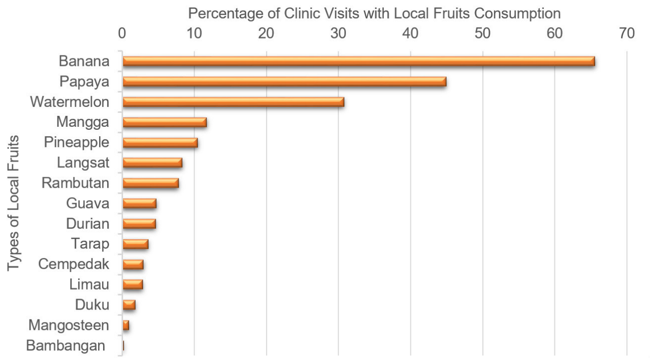

Figure 1: Most common local fruits consumed during study period (n = 109).

Association Between Number of Clinic Visits with Local Fruits Consumption and Number of INR Out of Range

In our study, number of clinic visits with reported local fruits consumption is significantly associated with the number of INR out of range, after adjustment for other variables. An increase in the number of clinic visits with reported local fruits consumption was associated with 8% higher number of INR out of range (IRR = 1.08, 95% CI 1.05,1.10, $p < 0.001$). This is the only predictor retained in the final regression model (Table 2).

Association Between Type of Fruits Consumed and Number of INR Out of Range

Based on simple NBR, the number of INR out range associated with local fruits consumption was significantly higher among patients who reported durian (IRR = 1.152, 95% confidence interval (CI) 1.004–1.322, $p = 0.043$), *tarap* (IRR = 1.237, 95% CI 1.051–1.456, $p = 0.010$), pineapple (IRR = 1.115, 95% CI 1.032–1.204, $p = 0.005$), *cempedak* (IRR = 1.278, 95% CI 1.025–1.594, $p = 0.029$), banana (IRR = 1.056, 95% CI 1.029–1.085, $p < 0.001$) and papaya (IRR = 1.048, 95% CI 1.016–1.081, $p = 0.002$) consumption (Table 2). Although papaya and banana may be the most popular local fruits, their contributions towards number of INR out of range were, nevertheless minimal.

Association between Number of Fruits Consumed and Number of INR Out of Range

In terms of number of types of local fruits consumed in the past one week, taking one type or more than one type of fruits both significantly affect the number of INR out of range (Table 2), based on simple NBR.

Table 2: Negative binomial regression.

Variable	Simple Negative Binomial Regression			Multiple Negative Binomial Regression		
	b	**Crude IRR (95% CI)**	**p**	**b**	**Adj. IRR (95% CI)**	**p**
Durian	0.1421	1.152 (1.004,1.322)	0.043			
Mango	0.0564	1.058 (0.966,1.158)	0.221			
Langsat	0.1246	1.132 (0.998,1.285)	0.054			
Orange	–0.0414	0.959 (0.788,1.166)	0.678			
Rambutan	0.0699	1.072 (0.949,1.210)	0.258			
Papaya	0.0475	1.048 (1.016,1.081)	0.002			
Banana	0.0552	1.056 (1.029,1.085)	< 0.001			
Mangosteen	–0.0735	0.929 (0.625,1.379)	0.716			
Duku	0.0113	1.011 (0.784,1.304)	0.930			
Tarap	0.2132	1.237 (1.051,1.456)	0.010			
Pineapple	0.1089	1.115 (1.032,1.204)	0.005			
Watermelon	0.0235	1.023 (0.987,1.061)	0.202			
Cempedak	0.2455	1.278 (1.025,1.594)	0.029			
Guava	0.0560	1.057 (0.940,1.189)	0.349			
Bambangan	–0.2777	0.757 (0.277,2.067)	0.588			
Number of clinic visits with reported local fruits consumption within past one week	0.0800	1.083 (1.057,1.109)	< 0.001	0.0800	1.083 (1.057,1.109)	< 0.001

(*continued on next page*)

Table 2: (*continued*)

Variable	Simple Negative Binomial Regression			Multiple Negative Binomial Regression		
	b	Crude IRR (95% CI)	p	b	Adj. IRR (95% CI)	p
Number of clinic visits with reported consumption of 1 type of local fruits only within past one week	0.0799	1.083 (1.029,1.140)	0.002			
Number of clinic visits with reported consumption of >1 type of local fruits within past one week	0.0582	1.059 (1.032,1.088)	< 0.001			

Note: Adj. IRR = adjusted incidence rate ratio; b = regression coefficient; p = *p*-value; The model reasonably fits well; model assumptions are met

The fitted negative binomial distribution showed balance distribution of predicted probabilities across the observed probabilities of number of INR out of range (Figure 2).

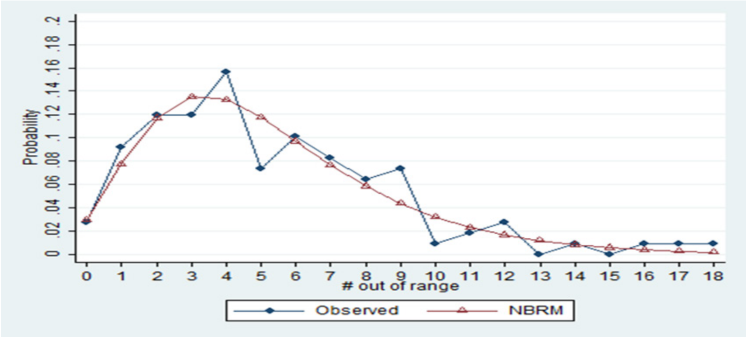

Figure 2: Comparison between observed to predicted probabilities value for number of INR out of range.

DISCUSSION

In this study, we aim to determine the association between local fruit consumption and number of INR out of range in NVAF patients. After adjustment of confounding factors, the only variable that affects the number of INR out of range is the number of clinic visits with reported local fruits consumption. Through simple NBR, our study reported significantly higher number of INR out of range among patients who reported durian, tarap, pineapple, *cempedak*, banana and papaya consumption during clinical visits. Consuming one or more than one type of local fruits both significantly affect the number of INR out of range.

Fruits contain many phytochemicals with the potential to cause clinically significant fruit-drug interactions, leading to diminished therapeutic effect or adverse events. The mechanisms behind such interactions are mostly related to phytochemical interference with the cytochrome P450 activity (Basheer and Kerem 2015; Kimura *et al.* 2010; Šarić Mustapić *et al.* 2018). The more potent S-enantiomer of warfarin is primarily metabolised by CYP2C9; with the involvement of other CYP450 enzymes in the metabolism process. (Attri 2020; Rulcova *et al.* 2010). Inhibition of the enzyme may potentiate warfarin effect. In a study investigating in-vitro inhibitory effects of fruit juices on CYP2C9, addition of fruit juices including bromelain-containing pineapple juice and papain-containing papaya juice showed reduction of the residual diclofenac 4'-hydroxylation and tolbutamide hydroxylation activity by human liver microsomes, both mediated by CYP2C9 (Hidaka *et al.* 2008). The results obtained from the study are in accordance with our result that pineapple and papaya are associated with INR out of range, likely due to enzyme inhibition. Our findings were also supported by a few literatures (Patel and Gohil 2008; Hu *et al.* 2022).

Other than direct metabolism-related interaction, local fruits may affect warfarin response through the alteration of human intestinal microbiome. There was a case report on warfarin interaction with banana flakes taken for diarrhea treatment which support the result of our study. The subsequent decrease in the rate and extent of diarrhea changed the patient's INR from therapeutic to subtherapeutic. This interaction may not directly attribute to interaction between banana and warfarin, but the effect of diarrhea-reducing activity of banana flakes on increased activity of vitamin K-producing intestinal flora and dietary vitamin K absorption, with subsequent reduction in INR (King and Strnad 2015).

Our study suggested that consumption of *cempedak*, *tarap* and durian is associated with higher number of INR out of range. Unfortunately, the studies on the fruits' interaction with warfarin are lacking. The association can probably be explained by the effect of fruits' phytochemicals contents on CYP450 enzymes. It was known that the flesh of the *cempedak* and *tarap* contains phytochemicals such as phenolic and flavonoid, but higher quantity was displayed in their peels and seeds (Abu Bakar *et al.* 2015). It is also worth mentioning that jackfruit, under the same genus (*Artocarpus*) as *cempedak* and *tarap*, was studied. The study concluded that jackfruit seed extract possesses anticoagulant and antiplatelet activity, by interfering with the intrinsic pathway of the blood coagulation cascade (Gangaraju *et al.* 2015). However, the type of phytochemical in the seed extract that contributes to the effect was not mentioned, and hence we could not relate if the effect applies to jackfruit pulp and the other two fruits of the same genus as well. Increment in risk of bleeding when taking jackfruit with drugs including warfarin was also described (Swami *et al.* 2012). Studies have also revealed that durian contains phytochemicals and the content varies among species (Ashraf *et al.* 2010; Juarah *et al.* 2021), it is thus possible that their effects on warfarin interaction, if any, vary among each other. Further studies are warranted to comprehensively evaluate the association between the consumption of these fruits and INR out of range.

Nevertheless, there are result from our study which contradict with the available literatures. Our study has concluded non-significant effect of mango consumption on INR out of range. Contrary to our finding, previous case report mentioned probable interaction between mango and warfarin, where daily mango ingestion averagely increased INR by 38% from baseline, followed by a 17.7% average INR decrease after removal of mango from diet for two weeks (Monterrey-Rodríguez *et al.* 2002; Izzo *et al.* 2005). The contradicting results may be attributed to the higher quantity of mango taken in the case report. Another literature also suggested that the vitamin A content in mango is responsible for the increasing anticoagulant effect when given at large doses, due to retinol and retinoid acid strong inhibition of CYP2C19 (Yamazaki 1999), which is responsible for the metabolism of warfarin R-isomer. Our study has also reported that mangosteen has not been significantly associated with higher number of INR out of range, although study described different xanthone components of the mangosteen fruit which were capable to inhibit multiple P450 isoforms, with the most potent inhibition observed for the CYP2C family of enzymes (Foti *et al.* 2009).

Limitations

First, this was a retrospective, observational, single centre study. Risk of 'recall biases' presents as patients may not be able to describe the fruits taken accurately; the use of pictorial chart in our study may have helped minimise but not entirely eliminated the issue. Second, there might be some unrecognised confounders which may contribute to subjects' deranged INRs, for instances the dietary vitamin K changes, traditional medicine usage, illnesses etc. In this study, we use multivariate analysis to determine the association between the variables, adjusting for the confounder.

Third, portions of the local fruits consumed by the study subjects were not properly measured, leading to missed outcome. Patients reported certain local fruits consumption may have taken them in small portion with negligible effect in their INRs, and hence risk of false negative association.

In this study, number of INR out of range was used as the measure of anticoagulation control associated with clinic visits with reported local fruits intake. However, TTR with Roseendal's method or percentage of INR in range (PINRR) are the established measure of anticoagulant control quality which have been advocated in clinical practice guidelines. The use of this measure can be considered for future study on similar topic, which may better translate to the safety and efficacy of warfarin.

There were also limited previous studies conducted on interaction between local fruits and warfarin to support our findings. Nevertheless, the result of this study has provided insights into the significance of this topic; it warrants clinicians to further enquire on local fruits consumption when assessing possible cause of deranged INR. It may also serve as a guide to form the hypothesis for future studies on the effect of local fruits consumption on patients' anticoagulation control quality. A multi-centred, prospective study can be performed to better generalise the results obtained.

CONCLUSION

Our study showed that increasing number of clinic visits with reported local fruits consumption is associated number of INR out of range with warfarin. There was a significant higher number of INR out of range among patients who reported durian, *tarap*, pineapple, *cempedak*, banana and papaya consumption during clinical visits; in terms of number of local fruits consumed, taking one or more than one type of local fruits both increase the number of INR out of range. This warrants clinicians to further enquire on local fruits consumption when assessing possible cause of deranged INR.

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