The Prevalence of Supratherapeutic International Normalised Ratio (INR) in Warfarin Use and Its Associated Factors among Atrial Fibrillation Patients in Hospital Teluk Intan, Perak

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Abstract

Introduction: Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. Data on the prevalence of supratherapeutic International Normalised Ratio (INR) following warfarin use among AF patients is only available for countries other than Malaysia. Malaysia is a multiracial country which might have different cultural behaviours. This difference might affect the different use of traditional medicines that contributes to supratherapeutic INR.

Objective: This study aimed to determine the prevalence of supratherapeutic INR in warfarin use and its associated factors among the AF patients.

Method: The study population consisted of patients who were diagnosed with AF, treated with warfarin and followed up in the warfarin clinic at Hospital Teluk Intan, Perak. Secondary data was retrieved from retrospective record review in the warfarin clinic at Hospital Teluk Intan, Perak. Logistic regression was used to predict the contributing factors of supratherapeutic INR.

Result: In total, 167 patients were included in the study. Of that, 79 patients (47.3%) were identified to have supratherapeutic INR in which bleeding occurrences happened in 23 patients (29.1%). Patients with heart failure were found to be 2.88 times more likely to develop supratherapeutic INR (OR=2.88; 95% CI: 0.89 to 9.39; p=0.078) than patients without heart failure. Besides, patients who were on regular methyl salicylate cream application were found to have 24.98 times higher risk of developing supratherapeutic INR (OR=24.98; 95% CI: 2.07 to 301.41; p=0.011). Based on HAS_BLED bleeding risk score, AF patients who belong to high-risk group, HAS_BLED score of ≥3, were 36.69 times more prone to supratherapeutic INR than patients who belong to non-high-risk group of HAS_BLED score <3 (OR=36.69; 95% CI: 12.87 to 104.64; p<0.001).

Conclusion: AF patients with heart failure, HAS_BLED score of ≥3 and using methyl salicylate cream should be closely monitored for the potential risk of supratherapeutic INR.

Keywords: INR, supratherapeutic, warfarin

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, which is characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function (1). One of the major clinical complications in AF is systemic and pulmonary embolisation. As a result of embolic risk, chronic oral anticoagulant, for example vitamin K antagonist, warfarin, is recommended for most AF patients to reduce AF related deaths (2). Although warfarin is proven to be an effective anticoagulant, it has a narrow therapeutic range which poses a challenge in the treatment of AF. The international normalised ration (INR), which is derived from the ratio between the actual prothrombin time and that of a standardised control serum, is used as a guide to adjust the doses of warfarin (1).

In the current setting, the therapeutic INR range for AF patients is 2.0-3.0 (3). A meta-analysis by Hart *et al*. (4) revealed that the adjusted dose of warfarin within the therapeutic range of INR (2.0-3.0) showed a significant 64% risk reduction in stroke and 26% reduction of all-cause mortality in patients with non-valvular AF. Supratherapeutic INR in AF is defined as an INR greater than the target range (5). One of the most common adverse reactions of supratherapeutic INR are haemorrhagic incidents. The risk of bleeding was evaluated in a cohort study of over 16,000 patients who have been diagnosed of AF between 2005 and 2010. The incidence of major bleeding with current, recent, past or no warfarin exposure was 3.8, 4.5, 2.7 and 2.9 per 100 patient-years, respectively (6).

In the late 1990s, clinically applicable stroke risk-stratification schemes in AF patients were developed in small cohort studies and had later been refined and validated in larger populations (7-11). The introduction of the CHA_2DS_2-VASc score has simplified the initial decision for oral anticoagulant in AF patients. The HAS-BLED tool was developed to provide a risk score to estimate the 1-year risk for major bleeding (12,13). It is of paramount importance to weigh between the clinical benefits and bleeding risks before initiating warfarin among the AF population. It should be a shared decision making between the physicians and patients on the initiation of warfarin.

A study by McGriff-Lee *et al*. (5) revealed that the prevalence of supratherapeutic INR in AF patients was 39%. This high percentage of supratherapeutic INR urged the researchers to study the prevalence of supratherapeutic INR following warfarin use among the AF patients in Malaysia, which was not available to date. Malaysia is a multiracial country that consists of Malay, Chinese, Indian and other races which might have different cultural behaviours compared to the other countries. Hence, the objective of this study was to determine the prevalence of supratherapeutic INR in warfarin use and its associated factors among AF patients in Hospital Teluk Intan, Perak.

Methodology

This was a retrospective record review using secondary data from the patients' medical records retrieved from the warfarin clinic of Hospital Teluk Intan, Perak. The warfarin clinic in Hospital Teluk Intan is managed by the medical officers and helped by the pharmacists who manage the warfarin Medication Therapy Adherence Clinic (MTAC). One of the main roles of MTAC pharmacists is to provide continuity and enhance patient care through education, monitoring, and close follow-up to patients who require warfarin therapy.

In this study, patients were included if they were treated with warfarin, attended the warfarin clinic in Hospital Teluk Intan from January 2017 to December 2017, started on warfarin for at least six months and older than 18 years old, whereas patients with missing data were excluded. Sample size was calculated using the formula with Finite Population Correction (Daniel WW, 1999), and the minimum number of samples needed to achieve in this study was 149. A standard data collection form was used to collect patients' demographic and clinical data, such as HAS_BLED score category, comorbidities, concurrent medications and use of over-the-counter medication, from the patients' medical records.

The prevalence of supratherapeutic INR events (INR > 3.0) and bleeding occurrences among the included patients from January 2017 to December 2017 were determined. The prevalence of supratherapeutic INR was calculated as the number of patients having at least one episode of supratherapeutic INR over the total number of patients who were included in the study during the one-year study period. Bleeding occurrences were the number (percentage) of patients with supratherapeutic INR who were presented with bleeding episodes.

Descriptive statistics were used to summarise the socio-demographic characteristics of patients. Continuous variables such as age were presented in mean and standard deviation for normally distributed data, or median and interquartile range (Q1, Q3) for data that are not normally distributed. Categorical data (gender, ethnicity, smoking behaviour, alcohol consumption, comorbidities, acute illness/acute infection at the time of supratherapeutic INR and concurrent medications) were presented in frequency and percentage. For the comparison between the two outcome groups (Supratherapeutic INR versus Non Supratherapeutic INR), Chi-square test was used for categorical variables, while t-test was used for continuous variables. A binary logistic regression was performed to analyse factors associated with supratherapeutic INR. Variables with $p<0.25$ were then included in the multiple logistic regression analysis.

Results

The medical records of a total of 368 patients were screened in the warfarin clinic. We excluded 201 patients who received warfarin for indications other than atrial fibrillation, patients with incomplete data and patients who were lost to follow up. As a result, a total of 167 patients were included in the study. According to the data reported in Table 1, 56.9% of the studied population constituted of male patients, and the ratio of male to female patients was 1.3:1. The mean age of the patients was 65.99 ± 9.12 years.

In this study, 79 patients (47.3%) were reported to have supratherapeutic INR, among which bleeding occurrences were found to happen in 23 patients (29.1%). A total of 65.2% these patients had gum bleeding, 30.4 % had haematuria and 4.3% had haemoptysis. Among the patients with supratherapeutic INR, the proportion between the male and female patients had no significant difference, with 54.4% and 45.6 % respectively. Malay ethnic had the highest percentage of supratherapeutic INR, 63.3% as compared to Chinese ethnic (26.6%) and Indian ethnic (10.1%). As shown in Table 1, variables found to be significantly different between supratherapeutic and non supratherapeutic INR were the HAS_BLED score category ($p<0.001$), heart failure ($p=0.033$), chronic kidney disease ($p=0.033$), and methyl salicylate cream use ($p<0.001$).

Among the factors analysed for the association with the risk of supratherapeutic INR, as presented in Table 2, smoking status, HAS-BLED score category, heart failure, chronic kidney disease, simvastatin and methyl salicylate cream use ($p<0.25$) were then subjected for multiple logistic regression. As for the factors of hepatic dysfunction, anemia, acute illness, paracetamol, NSAIDs, Tongkat Ali and ginseng variables, logistic regression analysis was not possibly done due to the lack of exposed patients in either of the comparison groups.

Patients who were on regular methyl salicylate cream application found to have 24.98 times higher odds of developing supratherapeutic INR (OR 24.98; 95% CI 2.07-301.41; $p=0.011$). Based on HAS_BLED bleeding risk score, AF patients who belong to high risk group, HAS_BLED score≥3, were 36.69 times more prone to supratherapeutic INR than patients who belong to non-high-risk group, HAS_BLED score of <3 (OR 36.69; 95% CI 12.87-104.64; $p<0.001$). Besides, patients with heart failure were found to be 2.88 times more likely to develop supratherapeutic INR (OR 2.88; 95% CI 0.89-9.39; $p=0.078$) than patients without heart failure.

Table 1: Baseline characteristic and factors associated with supratherapeutic INR in warfarin use among atrial fibrillation patients (n=167)

	Supratherapeutic INR (n=79)	Non Supratherapeutic INR (n=88)	Total (n=167)	p-value
Age, years, mean±SD	67.47±10.18	64.66±9.13	65.99±9.12	0.062*
Gender, n (%)				0.544#
Male	43 (54.4)	52 (59.1)	95 (56.9)	
Female	36 (45.6)	36 (40.9)	72 (43.1)	
Ethnicity, n (%)				0.937#
Malay	50 (63.3)	58 (65.9)	108 (64.7)	
Chinese	21 (26.6)	22 (25.0)	43 (25.7)	
Indian	8 (10.1)	8 (9.1)	16 (9.6)	
Smoking, n (%)				0.441#
Non smoker	64 (81.0)	64 (72.7)	128 (76.6)	
Ex-smoker	7 (8.9)	12 (13.6)	19 (11.4)	
Active smoker	8 (10.1)	12 (13.6)	20 (12.0)	
Duration of smoking, years, mean±SD	31.33±11.87	24.13±12.76	26.97±12.76	0.089*
Number of cigarettes per day, sticks, median (Q_1,Q_3)	10 (10,10)	10 (5,10)	10 (5,10)	0.789*
Alcohol consumption, n (%)				0.509#
Non alcoholic	77 (97.5)	86 (97.7)	163 (97.6)	
Ex- alcoholic	1 (1.3)	0 (0)	1 (0.6)	
Active alcoholic	1 (1.3)	2 (2.3)	3 (1.8)	
Warfarin starting dose, mg, median (Q_1,Q_3)	2.5 (2.0,3.0)	3.0 (2.0,4.0)	3.0 (2.0,3.5)	0.498*
Baseline INR, median (Q_1,Q_3)	1.9 (1.35,2.15)	2.0 (1.35,2.2)	1.97 (1.35,2.19)	0.950*
HAS-BLED score category, n (%)				**<0.001**#¥
Low risk	0 (0)	27 (30.7)	27 (16.2)	
Intermediate risk	6 (7.6)	38 (43.2)	44 (26.3)	
High risk	73 (92.4)	23 (26.1)	96 (57.5)	
Comorbidities, n (%)				
Rheumatic heart disease	5 (6.3)	10 (11.4)	15 (8.9)	0.256#
Heart failure	20 (25.3)	11 (12.5)	31 (18.6)	**0.033**#
Chronic kidney disease	8 (10.1)	8 (10.1)	10 (6.0)	**0.033**#
Hyperthyroidism	12 (15.2)	10 (11.4)	22 (13.2)	0.465#
Diabetic mellitus	23 (29.1)	21 (23.9)	44 (26.4)	0.442#
Hypertension	71 (89.9)	77 (87.5)	148 (88.6)	0.630#
Ischemic heart disease, n (%)	35 (44.3)	40 (45.5)	75 (44.9)	0.881#
Dyslipidaemia	16 (20.3)	17 (19.3)	33 (19.8)	0.880#
Cerebral vascular accident	18 (19.0)	16 (18.2)	34 (20.4)	0.461#
Concurrent medications, n (%)				
Proton pump inhibitor	7 (8.9)	9 (10.2)	16 (9.6)	0.765#
Ranitidine	20 (25.3)	22 (25.0)	42 (25.2)	0.962#
Simvastatin	55 (69.0)	53 (60.2)	108 (64.7)	0.205#
Antiplatelet	30 (38.0)	28 (31.8)	58 (34.7)	0.404#
Allopurinol	1 (1.3)	3 (3.4)	4 (2.4)	0.366#
Traditional medicines / Supplements / OTC medicines, n (%)				
Paracetamol	16 (20.3)	0 (0)	16 (9.6)	Undefined#
NSAIDs	17 (21.5)	0 (0)	17 (10.2)	Undefined#
Methyl salicylate cream	14 (17.7)	1 (1.3)	15 (9.0)	**<0.001**#
Tongkat Ali	3 (3.8)	0 (0)	3 (1.8)	Undefined#
Ginseng	3 (3.8)	0 (0)	3 (1.8)	Undefined#

* t-test; # Chi-square test (X^2); ¥ Post hoc bonferroni test were carried out to check on the significance lies among the low-risk, intermediate-risk and high-risk group of HAS_BLED score category. The results shown that there is significant difference between high-risk group and intermediate-risk group (p<0.001), and high-risk group and low-risk group (p<0.001).
Abbreviation: OTC – over the counter

Table 2: Binary logistic regression and multiple logistic regression analysis on the predictors of supratherapeutic INR among patients with atrial fibrillation (n=167)

Variable	Supratherapeutic INR (n=79)	Non Supratherapeutic INR (n=88)	Crude OR	95% CI	X^2 stat. (df)	p-value[a]	AOR	95% CI	X^2 stat. (df)	p-value[a]
Age	Not applicable	Not applicable	1.031	0.998,1.065	3.554 (1)	0.064				
Gender										
Male	43	52	1.00							
Female	36	36	1.209	0.655,2.234	0.369 (1)	0.544				
Ethnicity					0.131 (2)	0.937				
Malay	50	58	1.00							
Chinese	21	22	1.107	0.546,2.247	0.080 (1) [b]	0.778 [b]				
Indian	8	8	1.160	0.406,3.316	0.077 (1) [b]	0.782 [b]				
Smoking¶										
Non smoker	64	64	1.00							
Smoker	15	24	0.625	0.301,1.300	1.610 (1)	**0.208**				
Alcoholic¶										
Non alcoholic	77	86	1.00							
Alcoholic	2	2	1.117	0.154,8.121	0.012 (1)	0.913				
HAS-BLED score category¶										
Non-high-risk	6	65	1.00				1.00			
High-risk	73	23	34.384	13.183,89.768	84.182 (1) [b]	**<0.001**	36.69	12.87,104.64	45.39 (1) [b]	**<0.001** [b]
Rheumatic heart disease										
Yes	5	10	0.527	0.172,1.615	1.319 (1)	0.251				
No	74	78	1.00							
Heart failure										
Yes	20	11	2.373	1.055,5.335	4.555 (1)	**0.033**	2.88	0.89,9.39	3.11 (1) [b]	0.078 [b]
No	59	77	1.00				1.00			
Chronic kidney disease										
Yes	8	8	4.845	0.997,23.547	4.805 (1)	**0.028**				
No	71	80	1.00							
Hyperthyroidism										
Yes	12	10	1.397	0.568,3.438	0.532 (1)	0.466				
No	67	78	1.00							
Diabetic mellitus										
Yes	23	21	0.763	0.383,1.521	0.591 (1)	0.442				
No	56	67	1.00							

Table 2 (continue)

Variable	Supratherapeutic INR (n=79)	Non Supratherapeutic INR (n=88)	Crude OR	95% CI	X^2 stat. (df)	p-value[a]	AOR	95% CI	X^2 stat. (df)	p-value[a]
Hypertension										
Yes	71	77	1.268	0.482,3.332	0.234 (1)	0.629				
No	8	11	1.00							
Ischemic heart disease										
Yes	35	40	1.048	0.569,1.930	0.022 (1)	0.881				
No	44	48	1.00							
Dyslipidaemia										
Yes	16	17	0.943	0.440,2.021	0.023 (1)	0.880				
No	63	71	1.00							
Cerebral vascular accident										
Yes	18	16	1.328	0.624,2.825	0.543 (1)	0.461				
No	61	72	1.00							
Proton pump inhibitor										
Yes	7	9	0.853	0.302,2.410	0.090 (1)	0.764				
No	72	79	1.00							
Ranitidine										
Yes	20	22	1.017	0.505,2.048	0.002 (1)	0.962				
No	59	66	1.00							
Simvastatin										
Yes	55	53	1.513	0.796,2.876	1.615 (1)	**0.204**				
No	24	35	1.00							
Antiplatelet										
Yes	30	28	1.312	0.693, 2.484	0.696 (1)	0.404				
No	49	60	1.00							
Allopurinol										
Yes	1	3	0.363	0.037,3.565	0.862 (1)	0.353				
No	78	85	1.00							
Methyl salicylate cream										
Yes	14	1	18.738	2.403,146.149	16.157 (1)	**<0.001**	24.98	2.07,301.41	6.41 (1)[b]	**0.011**[b]
No	65	87	1.00				1.00			

a Likelihood Ratio (LR) test; b Wald test; ¶ Data is collapsed/merged for binary logistic analysis
Abbreviation: AOR – adjusted odds ratio, OR – odds ratio, CI – confidence interval

Discussion

It is worthwhile to note that the majority of AF patients on warfarin therapy in this study were male, making up 56.9 % of the patients, which is comparable to the similar study conducted by Son *et al*. (14) with 55.7%. Most of the patients included in this study were ranging from 57 to 75 years old, and most of them were non-smokers and non-alcoholics.

Among the comorbidities investigated, hypertension was found to be the most prevalent disease (88.6%) among AF patients. This finding is parallel with the data shown by Data Analytics CMMS 2011 (15), hypertension occupied the first place in the most common chronic comorbid among AF patients, which constituted 83.0% of those older than 65 years old and 81.1% of those younger than 65 years old (15). Hypertension is a strong risk factor for stroke in AF and appeared as an independent risk in CHA_2DS_2-VASc score. Uncontrolled high blood pressure increases the risk of stroke and bleeding events and may lead to recurrent AF. Therefore, good blood pressure control should be an integral part in the management of AF patients.

Most of the patients in this study have other comorbidities besides AF such as hypertension, ischemic heart disease and hyperlipidaemia. They were concurrently prescribed with medications other than warfarin. Precautions must be taken to avoid drug- drug interactions. The most commonly used concurrent medication was simvastatin, followed by antiplatelet, ranitidine and proton pump inhibitors. These results were in concordance with the comorbidities commonly found in the Malaysian population. Lipid lowering agents from the statin group are one of the important drugs used in the management of cardiovascular diseases based on the local and overseas guidelines. According to the Clinical Practice Guidelines Management of Type 2 Diabetes Mellitus (5th Edition) Malaysia, all patients over the age of 40 should be initiated with a statin regardless of the baseline LDL cholesterol level (16). Besides that, therapy with statins in patients with acute ST and non-ST elevation myocardial infarction reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization and stroke (17,18).

Pain relief medications were the most commonly used over-the-counter medications among our study population, which included paracetamol, NSAIDs and methyl salicylate cream. Considering that more than 90% of the patients were the elderlies above 65 years old, they were inclined to use these medications for fever and pain, particularly NSAIDs and methyl salicylate cream for arthritis pain. To avoid any potential drug interactions with warfarin, extensive counselling should be given to the patients and their caretakers to prevent supratherapeutic INR and subsequently the risk of bleeding.

The prevalence of supratherapeutic INR in this study was 47.3% as compared to the prevalence reported by McGriff-Lee NJ (from the eastern US) (5) which was 39.0%. One of the reasons was the older mean age in the supratherapeutic arm (67.5 years versus 56.0 years) observed in our study. This finding was supported by Froom *et al.* (19), whereby even after adjustment for other predictive factors, for every 10 years of increase in age, there was a 15% increase in the risk of supratherapeutic INR readings, which warranted a temporary cessation of warfarin therapy. Furthermore, it has been previously shown by Russmann *et al.* (20) that the steady- state warfarin dosage decreases with age and this is mainly due to a significantly reduced metabolic clearance in the elderly patients.

Next, in the present study, 23 patients were reported to have bleeding events. Fang MC *et al.* (21) and Pancholy SB *et al.* (22) in their respective study revealed that there was no gender difference in developing supratherapeutic INR and hence bleeding episodes in warfarin treated AF patients. These findings supported the outcome in the current study, where gender was not a significant factor in predicting the risk for supratherapeutic INR in this study. Smoking affects warfarin metabolism and causes deranged INR readings. In the current study, smokers were found to have a 60% lower risk of experiencing supratherapeutic INR as compared to non-smokers. Although this finding was not statistically significant, it was supported by a meta-analysis by Nathisuwan S *et al.* (23) where the investigators evaluated the effect of chronic cigarette smoking on warfarin metabolism.

Methyl salicylate cream use and HAS_BLED score category were found to be significantly different between patients with and without supratherapeutic INR. While heart failure is not a significant variable, it is included by the logistic regression because of its significant contribution to the risk of supratherapeutic INR in terms of pathophysiology. Methyl salicylate, an active ingredient in topical analgesic preparations, is commonly prescribed for ameliorating painful musculoskeletal disorders of various aetiologies. It is well known that methyl salicylate cream has drug-drug interaction when used concurrently with warfarin. In concordance with the known interaction, this study revealed that patients who used methyl salicylate cream had 24.98 folds higher odds to obtain at least one supratherapeutic INR. The

interaction between warfarin and methyl salicylate has been studied by Yip *et al*. among eleven patients. The Mean INR of the patients increased from 2.3 to 4.5 after a significant usage of topical methyl salicylate cream, which resulted in a positive alteration of the blood level of salicylate. Researchers postulated that methyl salicylate prolongs INR by depressing prothrombin formation in the liver (24). Also, methyl salicylate is known to be able to inhibit the synthesis of vitamin K-dependent clotting factors, hence displacing warfarin from protein binding sites. It leads to an increase in free drug level, followed by the risk of supratherapeutic INR (25).

In our study, patients who were in the high-risk HAS-BLED score category were found 36.69 times more prone to supratherapeutic INR. The HAS-BLED tool was developed to provide a risk score to estimate the one-year risk of major bleeding. Patients were evaluated based on their clinical characteristics, with the scores ≥3 classified as patients with a high risk of bleeding. These characteristics included hypertension (defined as SBP>160mmHg), abnormal renal function (the presence of chronic dialysis or renal transplantation or serum creatinine≥200µmol/L), abnormal liver function (chronic hepatic disease or biochemical evidence of significant hepatic derangement), stroke (previous history of stroke), bleeding, labile INR, elderly (age≥65), drug therapy (concomitant therapy such as antiplatelet agents, NSAIDs) and alcohol intake (consuming ≥8 alcoholic drinks per week) (12,13). Gallego *et al.* (26) conducted a prospective study to evaluate the usefulness of the HAS-BLED score in predicting both major bleeding and cardiovascular events in a cohort of anticoagulated patients with AF. Cox regression analysis showed that patients with HAS-BLED score ≥3 had an hazard ratio of 3.68 (95% CI 2.37 to 5.78; p<0.001). Nevertheless, cox regression analysis was not possible in the current study due to the absence of mortality data.

Heart failure has been found to interfere with INR stabilisation. Our patients with heart failure had 2.88 times higher odds of experiencing supratherapeutic INR compared to patients without heart failure. Although this is not a statistically significant observation, it is included by the logistic regression because of its significant contribution to the risk of supratherapeutic INR in terms of pathophysiology. This finding is supported by a cohort study by Visser *et al.* (27), which identified heart failure as an independent risk factor for excessive anticoagulation. Heart failure patients had a 1.5-fold to two-fold higher risk of INR>6. The increase in warfarin responsiveness and sensitivity is assumed to be the result of liver congestion. Both liver congestion and dysfunction are especially prominent during decompensated heart failure and most of the time, they are presented as hepatomegaly. In addition, the study by Hylek *et al*. (28) provided up to date evidence that heart failure exacerbation is associated with increased response to warfarin, by demonstrating a prolonged delay in the return of INR to within the therapeutic range after supratherapeutic INR. This group of researchers suggested oxygen limitation theory to be a plausible mechanism for the effect of heart failure on the excessive response to warfarin (28,29). Phase I drug metabolism by hepatic cytochrome P450 enzymes are directly dependent on oxygen supply. While there is no barrier to oxygen uptake by simple diffusion in the normal liver, in patients with liver impairment, there is reduced oxygen supply to hepatocytes. Therefore, in decompensated heart failure with an oedematous liver, oxygen diffusion to hepatocytes could be impaired, and warfarin metabolism could be reduced (28,29). This will then increase the risk of supratherapeutic INR in warfarin users.

The findings in this study are important to prevent supratherapeutic INR and subsequently haemorrhagic complications, by paying special attention to these risk factors when monitoring warfarin therapy. However, there were a few limitations in the current study. Firstly, the retrospective nature of the study was sensitive to potential human errors in the documentation of the medical records. The prospective exploration of the lifestyle and dietary details of the patients, which is an essential part of supratherapeutic INR assessment, was not possible. Due to the temporal limitation, convenient sampling instead of random sampling was used in this study. Convenient sampling was the contextual ideal choice when it was limited by the short research duration. Also, since the present study only involved a single institution, the results obtained may have limited generalisability to the Malaysian population.

Since AF is a disease with high economic impact and healthcare burden besides affecting the quality of life of the patients, effective management is needed to reduce the morbidity and mortality among AF patients. Therefore, there are some recommendations that can be made from this study. Firstly, the monitoring of time in therapeutic range (TTR) for warfarin should be implemented in the current setting to provide a better insight about the anticoagulation management of warfarin because TTR measures the percentage of time a patient's INR is within the desired treatment range or goal. As the monitoring of TTR is not routinely practised in the warfarin clinic of Hospital Teluk Intan, implementing this practice may better manage the risk of supratherapeutic INR and bleeding occurrences. Besides that, the

small sample size and single-centred design may have resulted in the statistically insignificance of some variables in the logistic regression, for example chronic kidney disease and the use of NSAID, which were demonstrated as the risk factors for supratherapeutic INR in other studies. In view of this, multi-centre study involving more hospitals in Malaysia can be carried out to generate meaningful evidence for the local population. The findings could then be used to create a model to predict the risk of supratherapeutic INR for every AF patient so that patients found to have high risk of supratherapeutic INR can be closely monitored or considered for the use of direct oral anticoagulants.

Conclusion

In this study, the prevalence of supratherapeutic INR was reported to be 47.3% with 29.1% bleeding occurrences. Logistic regression revealed that the factors that contributed to the supratherapeutic INR included HAS_BLED bleeding risk, heart failure and the use of methyl salicylate cream. It is of paramount importance to identify the contributing factors to achieve the goal of therapy in managing over-anticoagulation problems among AF patients treated with warfarin. Patients presented with these three risk factors should be reviewed more often and extensive counselling should be done not only to the patients but also to the caregivers.

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Conflict of Interest Statement

This study was not funded by any party. The authors declared that they have no known competing interests that could have appeared to influence the work reported in this paper.

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