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Research Article

THE PHARMACIST'S ASSESSMENT ON PATIENTS WHO CONSUME SUPPLEMENTS AND HERBAL WHILE UNDERGOING WARFARIN THERAPY

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ABSTRACT

Objective: The supplements and herbal medicines used should be monitored in a patient taking warfarin, to achieve the goal of warfarin anticoagulation. This study aims to evaluate the impacts of the supplement and the herbs used on the performance of anticoagulation.

Methods: There were 214 eligible patients for having $CHADS_2$ score >2 registered at warfarin-medication therapy adherence clinic coordinated by Cardiac Hospitals in Malaysia in 2012 included for this study. They have been assessed using a trained pharmacist regarding the safety and efficacy of warfarin as per guideline.

Results: Supplements and herbs are commonly used by the patient (61.2%) who is taking warfarin. Some patients (23%) have decided not to use or stop using it after being consulted by the pharmacist. Some are even starting to use it (37%). Effects of supplements and herbal medicines were found to decrease in the International normalized ratio (INR) reading as 33%, increasing in 37% the INR reading. Further, pharmacist action is to do a dose adjustment to reach INR in the therapeutic range 2.0–3.0. Supplements consumed as categorized as phytomedicine-containing herbs, such as Omega3 and glucosamine. Whereas herbs used as beetle leaves and the product of extracted herbs, for example, *Gingko biloba*, *Cordyceps*, etc.

Conclusion: Monitoring by pharmacist is needed to achieve the goal of warfarin as well as to minimize the INR out of therapeutic. The use of herbal and supplement is found to be a factor contributes to the performance of anticoagulation control which has been successfully achieved 71.2%.

Keywords: Supplement, Herbal medicine, Warfarin, International normalized ratio monitoring.

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INTRODUCTION

Patients with nonvalvular atrial fibrillation are recommended to use long-term oral anticoagulation with a Vitamin-K antagonist such as warfarin due to the risk of stroke. Atrial fibrillation is a cardiac disorder characterized by dysrhythmia. The number of patients tends to increase, in line with the increasing elder population. Atrial fibrillation has often been reported to be closely related to stroke; although the main treatment is actually to normalize the rhythm and rate of the heart and secondary to other factors such as age, gender, and other comorbid conditions, the treatment of atrial fibrillation is intended to prevent stroke [1].

Warfarin is effective for the secondary prevention for getting cardiovascular event by almost two thirds [2]. Warfarin is a Vitamin K-antagonist that inhibits the carboxylation activity so that the enzyme Vitamin K-epoxide reductase may reduce coagulation process [3]. Inhibition of Vitamin K-epoxide reductase complex 1 may block the clot formation. Therefore, stroke may be prevented by inhibiting clot formation. Recently known that clotting formation has individual variable due to genetic factors that attract researchers to investigate [4].

The significant interaction of the herbs and supplements in patients undergoing warfarin treatment has been widely reported. This reason is taken into account as the basis for warfarin monitoring. The effects of herbs and supplements are varies. The herbs or supplements containing hypericum extract had been found will interact with several drugs, including warfarin. The interaction of herbal constituent, such as *Gingko biloba* will result in variability of the International normalized ratio (INR) values, but it does not on pharmacokinetic or pharmacodynamic properties of warfarin [5].

The INR, the value is that used to indicate the coagulation profile, should be targeted to reach the therapeutic range of 2.0–3.0. However, a significant amount of patients who failed to achieve the target range is likely associated with poor anticoagulation either following the occurrences of clotting, bleeding or others.

Good INR control may reduce significantly the stroke and mortality [6]. In therapy with warfarin, INR monitoring is absolutely necessary. An INR value of more than 3.0 would be at risk of bleeding [7], whereas an INR value of <2.0 would be at risk of clotting. The target INR to be achieved is 2.0–3.0 as secondary prevention, warfarin is recommended for patients with atrial fibrillation who are at risk for stroke, either for moderate or high-risk stroke [8]. In Malaysia, the prevalence of atrial fibrillation was 2.8% and predicted will occur due to the lack of anticoagulation use [9].

Patient care models that use warfarin have been widely proven to provide better outcomes involving pharmacist in interprofessional collaboration [10].

Constructing on the patient's knowledge about the status of his illness is an essential component for the patient to reach the goal of therapy. The big role of the pharmacist should concern in patient education that expected to motivate patient to respond the warfarin therapy. Patients will be more assisted by the education by a pharmacist to achieve the desired outcome in such method of educating the patient showed that the uses of the booklet were effective for patients to gain the knowledge [11].

This study aims to identify the impact of pharmacist monitoring on the use of herbs and supplements on the achievement of the INR level. In addition, it evaluates whether the dose of intervention can compensate for the use of herbs and supplements to achieve the expected INR levels.

METHODS

Patients and medication therapy adherence clinic (MTAC) service

This is a cross-sectional study whose sampling technique was conducted convenient random sampling in patients enrolled for anticoagulation

therapy at the warfarin-MATC (W-MTAC) on the clinical day or consultation day. MTAC is a unit established by the ministry of health (MOH) of Malaysia that conducting patient consultations to improve patient adherence to the medication. W-MTAC is one of this unit that concern in anticoagulation with warfarin. This unit is performed by coordinated with the Cardiology Department and Pharmacists in charge are collaborated multidisciplinary with other health professionals.

Inclusion criteria

1. Atrial fibrillation diagnosed patients who agree to receive warfarin therapy in W-MTAC aged 18-year-old and above.
2. Patients having stroke risk factors based on the MOH clinical practice guidelines 2006 were measured using the $CHADS_2$ score.
3. Patients who were found to use herbs or supplements while undergoing warfarin therapy.
4. The patient should be informed about study purpose of this study understand and consent to this study.

Exclusion criteria

1. Patients in special condition such as pregnancy, patients with AIDS, pediatric, cancer, and clotting factor deficiency.

During data collection, the patient's assessment was performed in accordance with the protocol provided by MOH, which asked questions related to warfarin therapy that include herbal and supplement usage.

The initial and maintenance doses will be determined by the doctor must be taken daily (with food or on an empty stomach). The patient should take as soon as one remembers on the same day and not multiply the dose missed. Once a dose adjustment/intervention is performed, pharmacists will communicate with the doctor and then to inform patients about the appropriate warfarin dose. An indication of dose intervention such as after initiating warfarin on new or referral cases and after two consecutive blood tests in which the INR levels were nontherapeutic and for patients who had taken supplements, herbs or other interacting substances. The dose adjustment/intervention performed is to maintain INR in the therapeutic range and a blood test to monitor the INR level once patient scheduled for each consultation session during treatment. The pharmacist will adjust the dosage and patient advised to take warfarin prescribed by the doctor [12].

This study will describe about the approaches performed to solve the problems that caused by herbs and supplements consumption in W-MTAC. The pharmacist should play important role in achieving the goal therapy for such of patients, while the patients also to be encouraged to adhere to the regimen and schedule of warfarin appropriately, over the counter drug used, also to communicate with patients in how to take herbs and supplement, Vitamin K-rich food and physical activities.

As the measured variable is the INR which is read after the dose adjustment is done due to the consumption of herbs and supplements. The effectiveness of the intervention dose is the % time in the target range (% TTR) which is calculated using the Rosendhal formula. Analysis of TTR% is expected to measure the achievement of anticoagulation control of warfarin [6].

Sample size

The sample size determination yielded the adequate number of samples that obtained based on the data recorded in W-MTAC at cardiac Hospital, Malaysia a year before. It is about 2397 patients. Then, the required sample size was calculated using the Lwanga and Lemeshow formula:

$$n = \frac{Z_{1-\alpha/2}P\left(1-P\right)N}{d^2\left(N-1\right) + Z^2_{1-\alpha/2}P\left(1-P\right)}$$

This formula meet the term for limited sample size, where:
P = the anticipated proportion of the population.
= 50% is used to produce largest probability sample size can be obtained from which patient therapy to be fail or successful from the known population.
n = sample needed
N = population size
d = absolute precision required (0.10)
$Z_{1-\alpha/2}$ = number of standard error and the function of confidence level 95% [13].

Therefore, the minimum sample size is:

$$n = \frac{Z_{1-\alpha/2}P\left(1-P\right)N}{d^2\left(N-1\right) + Z^2_{1-\alpha/2}P\left(1-P\right)}$$

$$n = \frac{95\%\ 50\%\ \left(1-\ 50\%\right)2397}{\left(0.10\right)^2\left(2397-1\right) + \left(95\%\right)^2 50\%\ \left(1-50\%\right)}$$

n=93

RESULTS

The increase in service load at W-MTAC has reached 15.8% in 2011 at this hospital. The number of registered patients has reached 2397 patients, including 7.1% of newly diagnosed patients receiving anticoagulant therapy. Experienced and trained pharmacists are responsible for monitoring this unit between 4 and 8 years. Organizing training is conducted by State Health Department to ensure the quality of service in this unit.

The impact of warfarin dose on the patient's proflie will be showed in the following tables.

The performance of anticoagulation that had been achieved in this Hospital can be explained from the finding as shown in Fig. 1.

The INR value was a result from the laboratory investigation of the patients' blood sample. The blood samples were examined by the Department of Pathology, recorded and attached to the record for pharmacist in the MTAC on the same day of the consultation session. Fig. 2 is scattered plot of INR along the therapy. Between the two red lines are plotted the INRs that fall in the range of therapeutic.

Some of the supplements that were consumed by patients included supplement containing omega3; ginseng, *G. biloba*, glucosamine; *Cordyceps*, etc.

Hospital admission related to over-warfarinization were (5; 7.8%) and nonadmitted were 59; (25.8%). The cases that needed hospital admission included those with or without the onset of bleeding 41; (19.2%).

The most common supratherapeutic-related bleeding include bruises, gum bleeding and hematuria (34, 85%), and other bleeding (7, 15%). Patients with a history of stroke/transient ischemic attack (TIA) of (29; 15%) were those with high stroke risk categories. During this study, one of 10 patients who died was recorded due to AF-related intracranial hemorrhage.

The likelihood of the predictable variables (X_i) to influence the therapeutic outcomes (Y) had been analyzed using the logistic regression (enter method):

$$Y_1 = c + e^{\beta 1}X_1 + e^{\beta 1}X_2$$

Where:
Y_1 = Therapeutic or nontherapeutic INR
X_1 = Dose intervention performed by pharmacist
X_2 = Behaving herbal/supplement consumption
c = Constant.

The "omnibus tests of model coefficients" for examining the simultaneous effect of independent variable found in the model is

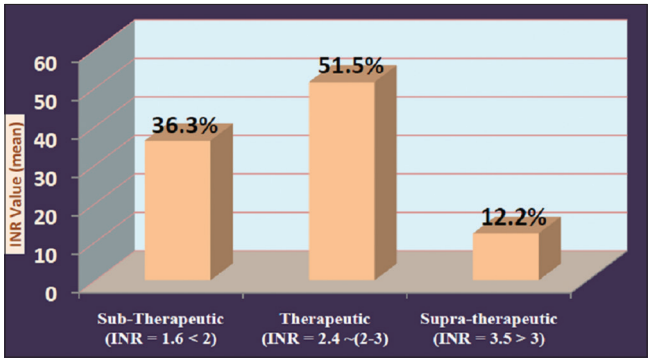

Fig. 1: The characteristic of the International normalized ratio (INR) value obtained from patients undergoing warfarin therapy. *INR value during a 1-year therapy (mean ± standard deviation) = 2.3±0.7

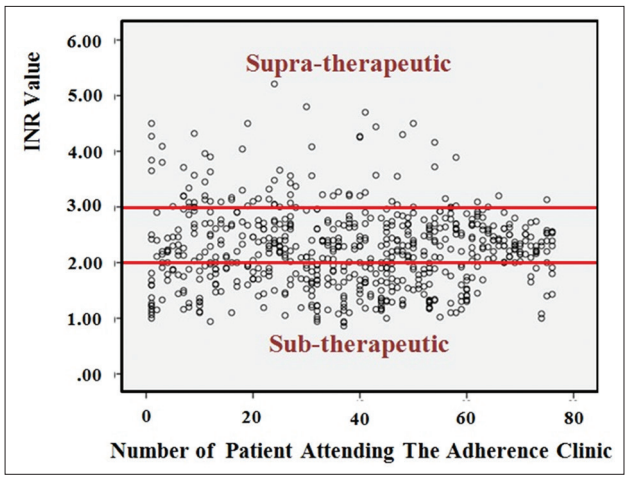

Fig. 2: The International normalized ratios during the therapy

significance in p=0.001, that is <0.05, therefore it will reject the H_0 in p=0.05. It indicates that there is (at least one) independent variable that applied simultaneously will contribute any change of the therapeutic outcome.

Summary of the Model will show the ability of the independent variable in explaining the change of dependent variable using the value of Cox and Snell R^2 and Nagelkerke R^2. These values are also called as Pseudo R^2. The value of Nagelkerke R^2 of 0.798 and Cox and Snell R^2 of 0.596 indicates that the ability of independent variables in explaining the dependent variable is 0.797 or 79.7% and there are 100–79.7% = 20.3% other factors which unable this Model to explain the contribution to the dependent variable.

The value of the Chi-square table for dF 2 at the p=0.05 is 5.99. The value of calculated Chi-square Hosmer and Lemeshow = 0.002 that is less than Chi-square table 5.99, also the significance value of p=0.999 >0.05 indicates that the model is acceptable and hypothesis testing can be done.

The accuracy of observations in the model is 93.6%, meaning that of n=644 observations, there are 603 observations have been classified appropriately by logistic regression models.

Partial test and model formation: The expectation of this test is to reject H_0 for predicting variables to be included in the model; the only significant variables can be substituted into the model. The requirement is to have significant value <α. There is one independent variable significantly affect the therapeutic outcome because the variable has a significance value <α=5%. The variable is X_2 = patient that behaves to take herbals and supplements (p=0.001) with a constant (p=0.001). The model is found as:

$$\Pi_i = \frac{\text{Exp}(-2{,}41 + 5.359x_{2i})}{1+\text{Exp}(-2{,}41 + 5.359x_{2i})}$$

Once the pharmacist did not to intervene dose (without dose intervention) a unit dose, then it makes the tendency of INR deviation to reach the therapeutic outcome become 0.556 times. In other words, if the pharmacist performs a dose intervention, the success of reaching the therapeutic level will be equivalent to 2-fold compared with no dose intervention. Patients who did not use herbs/supplements would achieve a therapeutic level of 269.727 times than those taking the herbs.

DISCUSSION

Atrial fibrillation patients are at risk of stroke. The stroke risk prediction as shown in Table 1 follows the $CHADS_2$ scheme. This scheme is simple and has been widely applied by doctors to predict the level of risk that the patient has. According to the $CHADS_2$ rule, stroke risk factors determining the level of risk are taken into account from the pre-existing conditions such as congestive heart failure (C); hypertension (H); age (A) of >75-year-old; diabetes mellitus (D) and previous stroke/TIA [15,16].

Schematic predictions on stroke have been investigated for its efficacy in recommending patients who at risk of stroke to receive preventive therapy. Patients at risk can be categorized based on $CHADS_2$ scoring. The $CHADS_2$ scheme categorizes patients' stroke risk as low-, intermediate-, and high-risk of stroke [17].

Stroke prevention in patients with atrial fibrillation is the secondary prevention, in which antiplatelet or anticoagulation agent is recommended according to patient own risk category [18]. Patients categorized as mild stroke risk (score <1) will be recommended to receive antiplatelet; those at intermediate risk (score 1–2) to receive combination with anticoagulant and those at high risk (score >2) are recommended receiving anticoagulants.

A unique finding has been discovered in this study. As listed in Table 3, the warfarin dose needed to maintain the INR level within the therapeutic range among races is characteristic. A significant difference occurs where higher doses need to be administered to Indian patients to maintain INR in therapeutic levels. As for the Malay and Chinese patients require a lower dose. Thus, warfarin dose also found to be interracial variable. Exactly similar to the finding obtained by Gan, *et al.* in 2003 [19].

However, the variabilitas of warfarin therapy occurred in this clinic. Fig. 1 shows the profile of INR monitored directly from patients' blood prior the consultation session in every clinic day. Off 51.5%, reaching therapeutic range, the mean of INR reading is 2.42 (between 2 and 3); sub-therapeutic value reached 36.3%, which is the mean value of INR of 1.6 or <2 and 12.2% is supra-therapeutic, the mean of INR value of 3.5 which is >3.

However, this is a rough calculation indicating that 51.5% of the measured INR is reaching range 2–3, but it does not mean that the anticoagulation control had been achieved is 51.5% as well. Hence, this data are less able to give adequate information about the quality of the control of the INR throughout the therapy.

Therefore, the benchmark for monitoring the quality of anticoagulation control, then used Rosendaal method, this rule has been widely used by researchers to obtain information about the INR value can guarantee the quality of anticoagulation of patients. The longer the INR period in the therapeutic range, the higher controlled the anticoagulation.

The parameter obtained from this anticoagulation control is called "TTR" or TTR. The unit for the TTR parameter is the percentage or the ratio at which the therapeutic INR is compared with the duration of anticoagulation therapy. The greater the value of this ratio or % TRR,

Table 1: Baseline characteristic of patients diagnosed with atrial fibrillation

Frequency, mean, SD and/or percentage		Value
Variable	**N=eligible patients**	**214**
Age (year-old)	Mean	64.6±11.3
Patient's distribution based on age (mean±SD); %	<75-year-old	(62.2±5.8); 77.1%
	>75-year-old	(79.2±3.2); 22.9%
Patient's distribution based on gender (%)	♂ Male	44.9
	♀ Female	55.1
Patient's distribution based on race (%)	Malay	54.7
	Chinese	40.2
	Indian	5.1
Type of atrial fibrillation (%)	Paroxysmal	14
	Chronic AF	86
*Stroke risk category	Mean±SD	2.3±1.1
	Intermediate	62.6%
	High risk	37.4%
Proportion of patients using herbs and supplements	76/214	35.5%

*The validation of clinical classification schemes for predicting stroke risk ccategories: <1 is low risk; (1–2) is intermediate; and>2 is high risk [14]. The status of the patients according to the rules of the $CHADS_2$ score: The amount of patients' comorbidity as confirmed by the doctor is added together, and thus, it would be the cumulative score. SD: Standard deviation

Table 2: The dose required (mg/week) to maintain therapeutic INR based on age group

Age group (year-old)	(Mean±SD)
<75	21.0±9.6
>74	14.0±6.6

*The (mean±SD) dose required (mg/week) to maintain the INR 2–3 is (19.9±9.6) mg/week. **The comparison of mean using the Mann–Whitney U test between the dose required to maintain INR 2–3 and two groups of age shows significant difference with Z=−9.626; P=0.001 (two-tailed) that is<0.05. SD: Standard deviation, INR: International normalized ratio

Table 3: Required warfarin n dose adjusted by Pharmacist in order to result in the n therapeutic level of INR

Race	Dose (mean±SD) (mg/week)
Malay	19.2±9.1
Chinese	19.3±9.6
Indian	25.8±14.2

*Kruskal–Wallis to test the dose differences in three races showed significant with λ^2: 11.163 and p: 0.004. SD: Standard deviation, INR: International normalized ratio

Table 4: The fluctuation of INR level caused n by the use of supplements and herbal

Type	↑increased INR	↓decreased INR	↔erratic INR
Supplement	35	32	29
Unidentified herbal	11	9	8
Herbal medicine	8	7	5

INR: International normalized ratio

the greater the quality of anticoagulation. This is the development of the method introduced by Rosendaal that is to measure the INR in the subject at a certain time between two consecutive levels is linear [20].

Interventions performed by pharmacists to control the factors affecting INR levels, such as developing dose manipulation. The dose manipulation or adjustment is performed to counter these interacting substances that potentially affect the INR levels.

Taking the herbs or supplements are advisable to maintain the regularity of the amount and time, so unable to identify the changes that occur at the level of INR. As shown in Table 4 that the use of supplements/herbs may cause the fluctuation of the INR level. The difficulties is faced due to the influence occurs unpredictably. Furthermore, conditions associated with preexisting comorbidity, and then pharmacist needs to emphasize the need to communicate effectively with patients.

Coagulation control results achieved in this study reached a good quality, which is the TTR (%TTR) of 71.2% [6]. The time in the target range that achieved 70% or more will be able to reduce the incidence of stroke significantly.

A report from the investigation of the anticoagulation service which is involving integrated pharmacist can improve the outcomes, especially in therapeutic INR control as well as within their target INR range. Monitoring services performed by pharmacists in warfarin clinic can reduce the complications associated with anticoagulation therapy at 63% TTR compared to that with usual care (55.2% TTR). Such monitoring is sufficient to support the services implemented by pharmacists [2].

The quality of anticoagulation had been achieved by the W-MTAC shown in Fig. 3. Most of the patients (81.1%) had received warfarin in a good quality control that experienced more than 60% TTR during therapy. It also means that pharmacists had monitored the anticoagulation therapy with a good performance. As reported by another investigation that a good performance had been achieved in other Hospital in Malaysia, reaching 68.3% TTR from patients whose high knowledge about warfarin therapy [21]. Given the significant relationship between patient's knowledge and the performance of anticoagulation control as reported in that study, it can be said that good performance will not be achieved unless otherwise with the sufficient knowledge. Similarly, pharmacists have played a good role in W-MTAC because they have been successful in providing adequate patient education. Proper education will improve knowledge and patient's adherent in warfarin therapy.

In this study, it has been found that analysis of factors contributing to the achievement of anticoagulation controls during warfarin therapy is as expected. Factors that may contribute significantly to the achievement of therapy are patient's non-adherence because of using herbs while performing warfarin therapy. The contribution is greater than the intervention factor performed by the pharmacist. Hence, however, the pharmacist's actions in monitoring warfarin therapy will be determined by the patient's own behavior. Similarly, pharmacists will be required to emphasize patients intensively to comply guidance of warfarin therapy.

Such results are very difficult to obtain if other determinant factor controls are ignored, the existing comorbidities, understanding, and compliance will also contribute as primary challenges that should

Table 5: The statistical correlation between dose intervention performed by the pharmacists and behaving supplements/herbal consumption

Variables	Spearman's rho
Dose intervention (X_1) versus herbal consuming (X_2)	Significant with r=−0.113 and P=0.004 (2 tailed)

INR: International normalized ratio

Table 6: The list of supplements and herbs found to cause increase in the INR level

Omega3 containing products: HPA capsule; fish oil combine with multivitamin and flaxseed oil
Chinese herbs mix/soup; Dong Guai
G. biloba (Nonselective MAO)
Other phytomedicine: Phytogreen and olivenol

INR: International normalized ratio

Table 7: The list of supplements and herbs found to cause decrease in the INR level

Fruit juice/extract Monavie; Acai berries and celery juice
Goat milk "Hi Goat"
Stichopus horrens: Gamat jelly
Alfa lipid supplement
Mahkota dewa (*Phaleria papuana*); Estetika (Pegaga) dari *Centela asiatica*
Tongkat Ali capsule (Caffeine)
Uric acid lowering agent: Niao Suan Yuan (gentiana radix mix with semen plantago)

INR: International normalized ratio

Table 8: List of herbs and supplement found to be erratic in measuring the INR level

Xangosteen (polyphenol); calcium; glucosamine/chondroitin supplement
Uric acid lowering agent: Niao Suan Yuan; gentiana radix, semen plantago
Herbal formulation: Rheum palmatum, *Cordyceps sinensis* fam ascomycete; semen prunus persia, cortex *Cinnamomum cassia*, radix *Glycirrhiza uralensus; Cordyceps* essence Lo Hong Ka; Dong Chong Cao (Tasly Brand)
Chlorophylls-containing products: Spirulina; Trienol E; EPO; Viatril; Alfalfa, Usana; AOpro (co-Q10); Flaxseed
Ginseng-containing products such as: Pharmaton, Pao Sum; Cao Gen Bai; Lin Wan; Cao Gen Bai Lin Wan from Radix Pseudoginseng, Fossila Oasis Mastodi
Danzen brand Ling Zhi (Ganoderma extract); Dan Shen Plus Capsule (Kasly); Margaret Plus contains *Glycine max* semen extract (Kasly)
Garlic (*Allium sativum*); cloves; Misai kucing: (*Orthosiphon aristatus); Ligusticum wallichii*; Habatus saudah (*Nigella sativa*, Linn.)

Phytomedicines: Stem cell enhancer capsule (AFA extract); EPO (hormonal balance capsule); biolife (nonacidic Vitamin C+bioflavonoid SR tablet); propolis

be covered by pharmacists to consult about the safety and efficacy of anticoagulation. Even though, patients had been well consulted, but unfortunately, the hemorrhagic event was still unresolved [22].

Pharmacists should also be able to convince doctors that the risk of thromboembolic is the basic reason and the tendency of patient noncompliance should be taken into consideration in warfarin therapy [23].

Other than those interacting substances mentioned in Tables 6-8, the kind of fermented foods such as BioNatto is found to increase in INR in this study. It contained rich of Vitamin K derivate has high bioavailability. It had been reported produce warfarin interactions in the previous study [5].

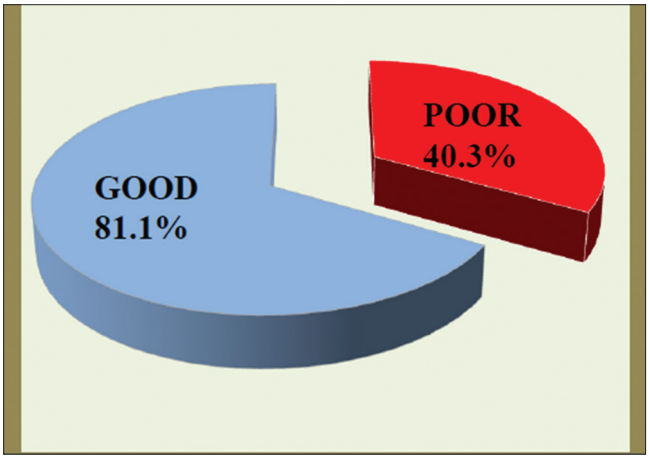

Fig. 3: Quality of the anticoagulation control (mean of % time in target range [TTR]). *(Mean ± standard deviation) of TTR is (71.2±2.1) %. *(Poor = %TTR <60% and good = %TTR >60%). Mann–Whitney U-test to compare the quality of the anticoagulation control achieved showed significant with Z: −10.309, p=0.001

Several marketed products such as ginger, ginkgo, green tea, saw palmetto; Dong Quai; salvia miltiorrhiza (Danzen), and cranberry juice are potentially cause drug interactions also found in this study [24,25]. Interactions will occur with several drug, and it might induce the INR variability significantly and result in major bleeding [26].

CONCLUSION

Monitoring by pharmacist is needed to achieve the goal of warfarin as well as to minimize the INR fall in supra- or sub-levels. The pharmacist monitoring may succeed the time in the target range of 71.3%.

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