A RETROSPECTIVE STUDY ON THE ASSOCIATION OF HAS-BLED SCORE WITH RISK OF GASTROINTESTINAL BLEEDING AMONG PATIENTS ON WARFARIN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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LIST OF ABBREVIATIONS, SYMBOLS AND ACRONYMS

HUSM	Hospital Universiti Sains Malaysia
GIB	Gastrointestinal bleeding
INR	International Normalized Ratio
UGIB	Upper gastrointestinal bleeding
LGIB	Lower gastrointestinal bleeding
VTE	Venous thromboembolism
VKA	Vitamin K antagonist
TTR	Therapeutic Therapy Range
AF	Atrial fibrillation
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly
ATRIA	Anticoagulation and risk factors in atrial fibrillation
HEMORR 2 HAGES	Hepatic or renal disease, ethanol abuse, malignancy, older age ≥75 years, reduced platelet count or function, re-bleeding risk, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, stroke
TARV	Transcatheter aortic valve replacement

NSAID	Non-steroidal anti-inflammatory drugs
CYP2C9	Cytochrome P450 family 2 subfamily C member 9
VKORC1	Vitamin K epOxide Reductase Complex subunit 1
Egfr	Estimates glomerular filtration rate
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
GARFIELD-AF	Global Anticoagulant Registry in the Field-Atrial Fibrillation
CHA2D2VASC	Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke, Vascular disease, age 65 to 74 and sex category (female).
ABC	Age, biomarker, clinical history
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase

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ABSTRAK

Latar belakang: Warfarin ialah antikoagulan antagonis vitamin K oral yang telah digunakan untuk sindrom antifosfolipid, penggantian injap prostetik,pencegahan strok dalam fibrilasi atrium (AF) dan rawatan thromboembolisme. Ia telah digunakan secara meluas di seluruh dunia terutamanya di negara membangun kerana kos dan ketersediaannya yang rendah berbanding anticoagulant oral novel yang lain. Walaupun manfaatnya yang sangat berguna, komplikasi seperti pendarahan besar terutamanya pendarahan usus (GIB) adalah penting untuk dicegah lebih awal. Skor HAS-BLED digunakan sebagai alat penilaian pendarahan kepada pesakit sebelum menerima warfarin, dan faktor risiko penting yang menyumbang kepada GIB boleh dikenal pasti dan dipantau dengan teliti. Bagaimanapun, insiden dan faktor risiko GIB pada pesakit yang menerima warfarin tidak didokumenkan dengan baik di Malaysia.

Objektif: Kajian ini bertujuan untuk menilai keberkesanan skor HAS-BLED dalam meramal kejadian GIB dalam kalangan pesakit yang menerima warfarin di Hospital USM.

Kaedah: Di dalam kajian retrospektif ini, data pesakit yang menerima rawatan warfarin dan di bawah rawatan susulan Hospital USM dari bulan Januari 2017 sehingga bulan Disember 2021 telah dikaji. Pesakit dibahagikan kepada kumpulan berisiko tinggi (HAS-BLED ≥3) dan kumpulan tidak berisiko tinggi (HAS-BLED ≤2). Perkaitan antara skor HAS-BLED dan GIB ditentukan dengan menggunakan simple

logistik regression diikuti dengan multiple logistik regression untuk faktor yang dikaitkan dengan GIB.

Keputusan: Sejumlah 138 orang pesakit yang menerima rawatan warfarin di Hospital USM telah dimasukkan dalam kajian ini dan kejadian GIB adalah seramai 25 orang pesakit (18.1%). Bilangan pesakit yang mendapat GIB dalam tempoh dan selepas enam bulan menerima warfarin masing- masing adalah 16 orang (64%) dan 9 orang (36%). 24 pesakit (96%) dari kumpulan berisiko tinggi (skor HAS-BLED ≥3) mendapat GIB dan seorang pesakit sahaja dari kumpulan tidak berisiko tinggi (skor HAS-BLED ≤2) mendapat GIB. Hasil kajian ini menunjukkan perkaitan signifikan antara skor HAS-BLED dan GIB (***P***<0.001). Enam faktor risiko penting yang dikaitkan dengan GIB telah dikenal pasti iaitu fungsi buah pinggang yang tidak normal, fungsi hati yang tidak normal, strok, kecenderungan pendarahan, bacaan International Normalized Ratio (INR) yang tidak stabil and umur (***P***<0.05).

Kesimpulan: Skor HAS-BLED sesuai untuk meramalkan kejadian GIB dikalangan pesakit yang menerima rawatan warfarin di Hospital USM. Skor HAS-BLED yang tinggi (HAS-BLED ≥ 3) dikaitkan dengan peningkatan kejadian GIB dikalangan pesakit yang menerima rawatan warfarin. Kajian lanjut adalah sangat diperlukan untuk membuktikan keberkesanan skor HAS-BLED dalam meramalkan kejadian GIB dikalangan pesakit yang menerima rawatan warfarin.

Kata Kunci: *Gastrointestinal bleeding, International Normalized Ratio, Warfarin.*

ABSTRACT

Background: Warfarin is an oral vitamin K antagonist anticoagulant used for antiphospholipid syndrome, prosthetic valve replacement, stroke prevention in atrial fibrillation and treatment for thromboembolism. It has been widely used worldwide, especially in developing countries, because of its low cost and availability compared to other novel oral anticoagulants. Despite its valuable benefits, complications such as major bleeding, particularly gastrointestinal bleeding (GIB), are essential to prevent early. The HAS-BLED score is used as a bleeding assessment tool in patients before receiving warfarin, and significant risk factors contributing to GIB can be identified and closely monitored. However, the incidence and risk factors for GIB in patients who receive warfarin are not well documented in Malaysia.

Objectives: This study aims to evaluate the effectiveness of the HAS-BLED score in predicting GIB events in patients taking warfarin at Hospital USM.

Material and Methods: In this retrospective study, the data of patients receiving warfarin treatment and undergoing follow-up at Hospital USM between January 2017 and December 2021 were retrieved. The patients were categorized into a high-risk group (HAS-BLED score ≥ 3) and a non-high-risk group (HAS-BLED score ≤ 2). The association between the HAS-BLED score and the occurrence of GIB was determined using simple logistic regression followed by multiple logistic regression.

Result: A total of 138 patients who received warfarin at HUSM were included in this study and the proportion of GIB was 25 patients (18.1%). The number of patients with GIB within and after six months of warfarin therapy was 16 and 9, respectively. 24 patients (96.0%) who were from the high-risk group (HAS-BLED score ≥3) had GIB and only one patient from the non-high-risk group (HAS-BLED score ≤2) had a GIB event. The outcome of this study denoted a significant association between the HAS-BLED score and GIB ($P<0.001$). Six significant risk factors associated with GIB were identified, including abnormal renal function, liver function, stroke, bleeding tendency, labile INR, and age ($P<0.05$).

Conclusion: The HAS-BLED score adequately stratifies or predicts GIB events among patients who received warfarin in Hospital USM. A high HAS-BLED score (≥3) was associated with increased GIB events among patients on warfarin therapy. Further studies can help to establish the diagnostic performance of the HAS-BLED score in predicting GIB among patients on warfarin.

Keywords: *Gastrointestinal bleeding, International Normalized Ratio, Warfarin*

CHAPTER 1: BACKGROUND

1.1 Introduction

Gastrointestinal bleeding (GIB) is a potentially life-threatening event and one of the most common medical emergencies. It is associated with significant morbidity and mortality. The mortality rate for acute upper gastrointestinal bleeding (UGIB) is about 5–10%. Despite developments in healthcare, new intervention strategies such as endoscopy and improvements in intensive care units and surgical management, the mortality rate did not improve much (Aljarad and Mobayed, 2021). Based on thirty years (1987-2016) incidence study of GIB in Finland, the overall crude incidence rate of GIB was 1.74 per 1000 person-years (95% CI, 1.64-1.85) (Vora et al., 2020).

GIB remains a significant cause of emergency visits, leading to hospital admission with an estimated incidence of about 100 per 100 000 hospitalizations and is associated with significant morbidity and 30-day mortality (Monteiro, 2016). Furthermore, in Western countries like the United States and the United Kingdom, annual hospital admissions for GIB have been estimated at up to 150 patients per 100000 population with a mortality rate of 5%-10% (Kim, 2014).

Many factors contribute to the incidence of GIB, including warfarin usage. Warfarin has been widely used worldwide, particularly in developing countries such as Malaysia, because of its low cost and availability compared to other novel oral anticoagulant (Lee et al., 2021). It reduces the incidence of thromboembolism but increases the risk of GIB. Warfarin is an oral vitamin K antagonist anticoagulant

and it produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3-epoxide (vitamin K epoxide) (Chen et al., 2014). It is widely used to prevent cardioembolic stroke in atrial fibrillation, treat venous thromboembolism, antiphospholipid syndrome and prosthetic valve replacement. (Tadros and Shakib, 2010).

Major bleeding events, including GIB are among the concerns of warfarin usage. Morbidity and mortality from warfarin-induced GIB are related to various risk factors. Therefore, the European Society of Cardiology recommended a formal risk score for assessing bleeding among patients with atrial fibrillation. It was a novel, user-friendly scoring system known as the HAS-BLED score. It helps to address modifiable bleeding risk factors and identify patients at high risk of bleeding. HAS-BLED score measures the risk of bleeding using clinical and laboratory characteristics: hypertension, abnormal renal/liver function, stroke, history of bleeding predispositions, labile INR, elderly (>65 years) and drugs/alcohol use (Hindricks et al., 2021).

Apart from risk estimation of major bleeding in patients with atrial fibrillation on anticoagulants, HAS-BLED score has also been validated for bleeding risk assessment in patients with acute venous thromboembolism (VTE) during Vitamin K antagonist (VKA) treatment. Acute VTE patients are classified as high-risk bleeding (HAS-BLED score ≥ 3) and non-high-risk bleeding (HAS-BLED score ≤ 2). Acute VTE patients with a higher HAS-BLED score warrant correcting any potentially reversible risk factors for major bleeding and careful INR monitoring (Kooiman et al., 2015).

Other than the HAS-BLED score, several other scoring systems are used for bleeding risk assessment before or during anticoagulant treatment. Examples of such assessment systems include HEMORR 2 HAGES: (hepatic or renal disease, ethanol abuse, malignancy, older age ≥75 years, reduced platelet count or function, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factors, excessive fall risk, stroke) and ATRIA (anticoagulation and risk factors in atrial fibrillation: anaemia, renal disease, elderly age ≥75 years, any prior bleeding, hypertension). The systemic review and meta-analysis showed that the HAS-BLED score performs better than other HEMORR2HAGES and ATRIA in predicting bleeding risk in anticoagulated patients, simple and easy to apply (Zeng et al., 2020).

HAS-BLED was chosen in this study compared to other scoring systems such as ATRIA or HEMORR2HAGES because it has been used in many clinical trials since 2011, and the predictive performance of major bleeding is better compared to others (Apostolakis et al., 2012; Beltrame et al., 2017). Apart from that, there are limited data in Asia Cohorts, and most of the data for HAS-BLED validation was done in several population cohorts, mainly from Europe (Roldán et al., 2013). A retrospective study was conducted by Universiti Putra Malaysia on the safety and efficacy of dabigatran versus warfarin in Asian patients with atrial fibrillation in Hospital Serdang. Effective outcomes showed lesser occurrence of ischemic stroke in the Dabigatran group (1.3%) compared to those in the Warfarin group (2.7%). Safety outcomes revealed lesser bleeding events in the Dabigatran group (6.7%) than those in the Warfarin group (14.7%). Stroke risk was measured via the CHA2DS2-VASc score, and bleeding risk was measured via the HAS-BLED score for newly diagnosed nonvalvular atrial

fibrillation before the counsel and start of oral anticoagulant. A high HAS-BLED score increases the patient's risk for major bleeding (Mat et al., 2020).

The sensitivity and specificity of the HAS-BLED score were studied in a tertiary care centre at AJ Institute of Medical Sciences in South India involving 100 patients on warfarin therapy for atrial fibrillation who presented with major bleeding manifestations between September 2017-2018. They found that the sensitivity was 80% and specificity was 68%. The positive and negative predictive values of HAS-BLED values were 71.4% and 77.27%, respectively (Balkrishna and Rai, 2019). Besides, our population's knowledge regarding oral anticoagulant and bleeding risk also remains low. Therefore, this study must be done on our people to see the practice of using the HAS-BLED score and the objective evidence of GIB as the complications of warfarin usage.

With knowledge of patients' bleeding risk based on the HAS-BLED score, the attending team can take extra preventive measures, such as arranging closer INR monitoring for patients who are in the high-risk group to prevent significant bleeding and mortality. The HAS-BLED score allows clinicians to objectively discuss their risk of bleeding with anticoagulant therapy with patients. It enables them to decide about initiating, continuing, or halting anti-coagulant treatment. The treating team may also identify patients at risk of bleeding without stopping anticoagulation therapy and offer an alternative oral anticoagulant like a novel oral anticoagulant (NOAC).

This study aims to evaluate the association between HASBLED score and the risk of warfarin-induced GIB, whereby a high HASBLED score ≥3 will likely cause bleeding. This study also aims to determine the most significant risk factors related to warfarin-induced GIB, allowing clinicians to initiate timely monitoring and intervention. Thus, reducing the risk of GIB and counselling patients for novel oral anticoagulants if they have a high HAS-BLED score ≥3. Based on this information, they can be placed under closer monitoring to reduce GIB events. This study's data may also guide clinicians in spending local health budgets on safer anticoagulants.

1.2 Objective

1.2.1 General Objective:

To determine the risk of gastrointestinal bleeding using the HAS-BLED score as a bleeding risk stratification among patients on warfarin in Hospital USM.

1.2.1 Specific Objectives:

1. To determine the proportion of GIB among patients on warfarin in Hospital USM.
2. To evaluate the association of high HAS-BLEED score ≥3 with risk of GIB in Hospital USM.
3. To identify significant risk factors associated with GIB among patients on warfarin in Hospital USM.

1.3 Hypothesis

A high HAS-BLEED score ≥3 is associated with an increased risk of GIB in Hospital USM.

1.4 Research Questions

1. What is the proportion of GIB among patients who received warfarin in Hospital USM?

2. Is a HAS-BLED score ≥3 associated with a high risk of GIB among patients who received warfarin in HUSM?

3. Which risk factors (hypertension, abnormal renal, abnormal liver function, stroke, bleeding tendency, labile INR, elderly and drugs) are significant in causing GIB among patients on warfarin in Hospital USM.

CHAPTER 2: LITERATURE REVIEW

Warfarin is one of the choices of oral anticoagulants commonly used to prevent and treat thromboembolism. The use of warfarin is limited by its narrow therapeutic interval, which necessitates frequent monitoring and dose adjustments. However, warfarin is an effective and relatively safe drug when maintained within the therapeutic range [(TTR) >60%](Lee et al., 2021). One of the significant complications of warfarin usage is GIB, a major contributor to global health issues. GIB events can be classified as overt, occult, or obscure. Overt or acute GIB manifest as hematemesis, coffee-ground emesis, melena, or haematochezia. American Gastroenterological Association defines occult GIB as the initial presentation of a positive faecal occult blood test result and or iron deficiency anaemia when there is no evidence of visible blood loss. Obscure GIB refers to recurrent bleeding in which a source is not identified after upper endoscopy and colonoscopy (Kim, 2014). A Standardize bleeding definition for cardiovascular trials was introduced, which was Bleeding Academy Research Consortium. It was hierarchically graded and consensus classification for bleeding (Mehran et al., 2011).

Several clinical risk prediction scores have been developed to help clinicians plan their follow-up and monitoring for patients on oral anticoagulants. The HAS-BLED score is an acronym for the assessed risk factors: H-Hypertension, A-Abnormal renal and liver function, S-Stroke, B-Bleeding, L-Labile INR, E-Elderly and D-Drugs or alcohol is one of the prediction tools that has been used to measure the risk of bleeding. HAS-BLED score was first proposed in 2010 as an estimation tool for the 1-year risk of major bleeding (intracranial, hospitalization, haemoglobin decrease 2 g/L, and/or transfusion) in a cohort of patients with atrial fibrillation (AF). It involved 3978

patients, an extensive population database from the Euro Heart Survey on atrial fibrillation collected between 2003 and 2004. 1.5% of major bleeding occurred during 1-year follow-up, and the annual bleeding rate increased with increasing risk factors. Prior major bleeding is the most significant clinical factor for major bleeding, with an odd ratio of 7.51 ($p<0.0001$) (Pisters et al., 2010).

Because of its simplicity and usefulness, this score is a practical tool in everyday clinical practice when deciding on starting oral anticoagulants for patients with AF and newly diagnosed acute coronary syndrome who need to be on antiplatelet therapy and anticoagulant therapy. HAS-BLED bleeding risk scheme is simple and focused on modifiable risk factors of bleeding. Generally, high bleeding risk score should not be a cause for withholding anticoagulant treatment. Instead, the identified bleeding risk factors should be monitored closely (Kirchhof et al., 2016). Even though the HAS-BLED score assesses bleeding risk in general and does not explicitly look into gastrointestinal bleeding, most bleeding events as a complication of anticoagulant use occur in the gastrointestinal tract (Pipilis et al., 2014).

Other than the HAS-BLED score, several other scoring systems are used for bleeding risk assessment before or during anticoagulant treatment. Examples of these assessment systems include HEMORR 2 HAGES: (hepatic or renal disease, ethanol abuse, malignancy, older age [≥75 years], reduced platelet count or function, re-bleeding risk, hypertension [uncontrolled], anaemia, genetic factors, excessive fall risk, stroke) and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation: anaemia, renal disease, elderly [age ≥75 years], any prior bleeding, hypertension). HAS-BLED remains an ideal assessment tool compared to other scoring systems

because of its balanced predictive sensitivity and specificity values. It is a widely applied assessment score, simple and very easy to implement in clinical settings (Chang et al., 2020).

HAS-BLED score can be used as a bleeding risk assessment in other conditions besides anticoagulated atrial fibrillation patients. It can also identify patients at high risk of developing major bleeding in acute venous thromboembolism while on anticoagulant treatment. Cumulative incidences of major bleeds were 1.3% in the non-high (HAS-BLED ≤2) and 9.6% in the high-risk group (HAS-BLED ≥3). Abnormal renal function and a history of bleeding events were independent predictors of significant bleeds during follow-up (Kooiman et al., 2015). This scoring system has also been validated in dual antiplatelet patients after receiving drug-eluting stents. Death and major bleeding were higher in the high HAS-BLED score group than in the low HAS-BLED score group (Konishi et al., 2015). The HAS-BLED score can also be used as a predictive tool for mortality and bleeding following TAVR (Transcatheter aortic valve replacement). A high HAS-BLED score (≥3) was a significant predictor of major and life-threatening bleeding after TAVR (Monirah et al., 2022).

Using the HAS-BLED score, we can identify significant risk factors that contribute to bleeding events; therefore, it has been validated as a tool for assessing the risk of bleeding worldwide. However, most of the data has come from Caucasian populations. Bleeding risk has been shown to differ across ethnicity. Apart from race, socioeconomic status should also be considered in bleeding risk assessments to guide the use of antithrombotic medication to manage AF and cardiovascular disease. Māori and Pacific people have a higher risk of developing most bleeding types than

Europeans. Indian, Chinese, and other Asians were at increased risk of intracranial bleeds compared to Europeans across most subgroups. Increasing socioeconomic deprivation was also connected to a higher risk of significant bleeding across most bleeding types or subgroups (Tse et al., 2021). Unfortunately, there are limited data on Asian cohorts. One evaluation study showed that among Malaysians who are on anticoagulants and developed clinically relevant bleeding events, the highest contributor to bleeding was GIB (Beshir et al., 2018).

This study aims to research the reliability of the HAS-BLED score as a tool for assessing the risk of GIB in an Asian population, specifically in Hospital USM who is receiving warfarin as anticoagulant therapy for all indications, not only atrial fibrillation. Therefore, the attending clinician can initiate close monitoring and proper intervention, especially in high-risk group patients, to reduce the risk of GIB in warfarin therapy patients.

2.1 Conceptual Framework

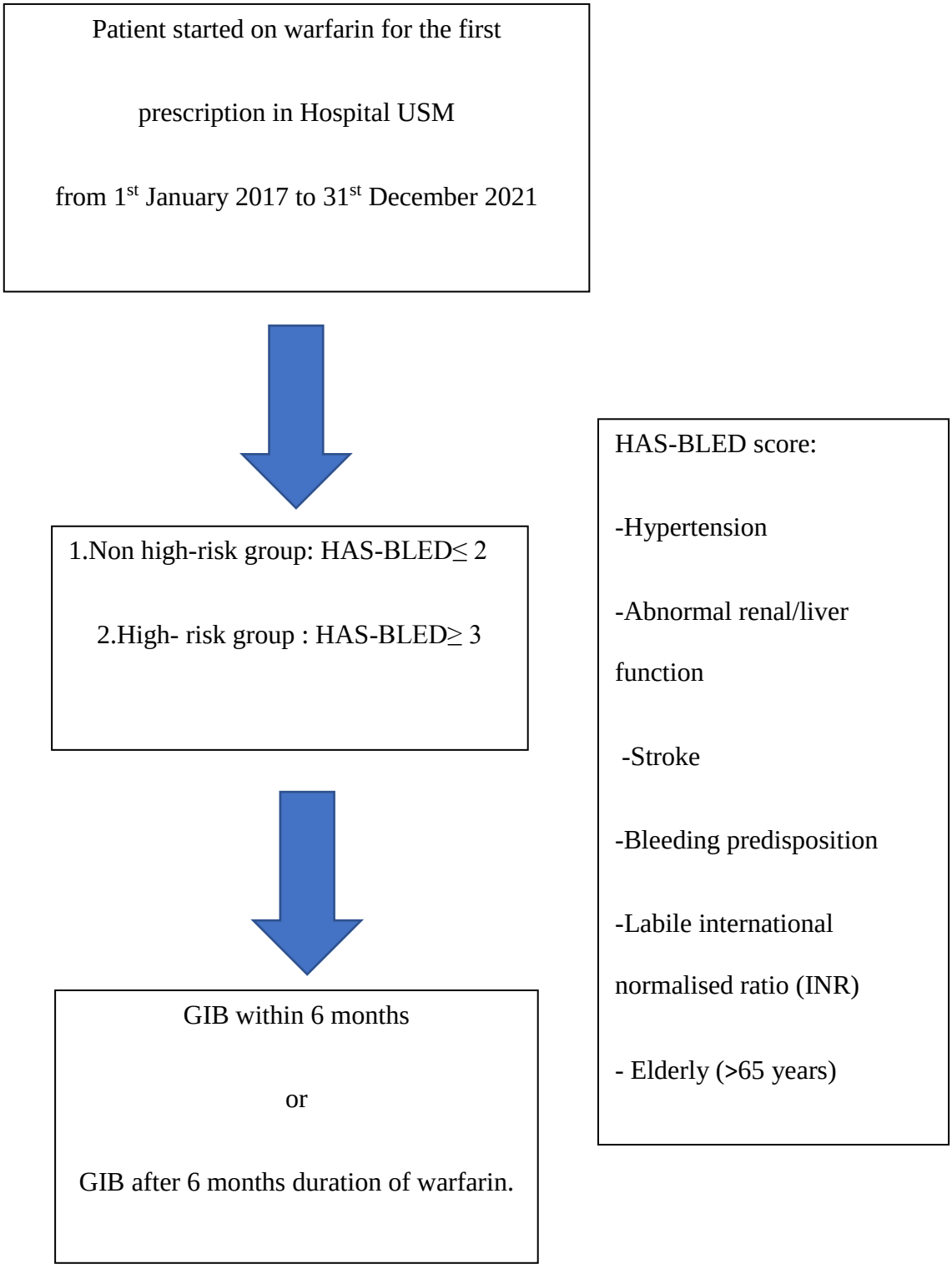


Figure 1: Conceptual Framework

2.2: Rational of Study

GIB is the most common bleeding condition resulting from warfarin use. It often necessitates hospital admission for intervention and monitoring and contributes to morbidity and mortality, increasing the burden on healthcare resources. HAS-BLED score is an established tool for assessing the risk of bleeding among patients on anticoagulant treatment. However, data is lacking on the effectiveness of the HAS-BLED score in evaluating the risk of GIB in patients on warfarin for any indications, not only atrial fibrillation specifically, in HUSM.

This study was conducted to ascertain whether the HAS-BLED score can significantly stratify patients into high-risk or non-high-risk of GIB in HUSM. In our clinical practice, the HAS-BLED score is only widely used in atrial fibrillation patients on warfarin to predict the risk of significant bleeding. By proving the effectiveness of the HAS-BLED score as a tool for predicting GIB, we propose that the HAS-BLED score not be limited to use in atrial fibrillation only. It may be utilised for other indications such as pulmonary embolism, antiphospholipid syndrome, post-mechanical valve replacement and others.

Another practical outcome that we hope to achieve with this study is to see a reduction in the number of warfarin-related GIB cases. By applying the HAS-BLED score for all indications and providing close monitoring and prompt intervention when indicated for high-risk group patients, we can prevent serious complications and improve patients' quality of life and survival rate.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This retrospective cohort study was conducted in Hospital USM, Kubang Kerian, Kelantan, from August 2022 until December 2022. Data collection was involved from 1st January 2017 until 31st December 2021.

3.2 Sample Area

The study included the medical clinic Hospital USM.

3.3 Study Population

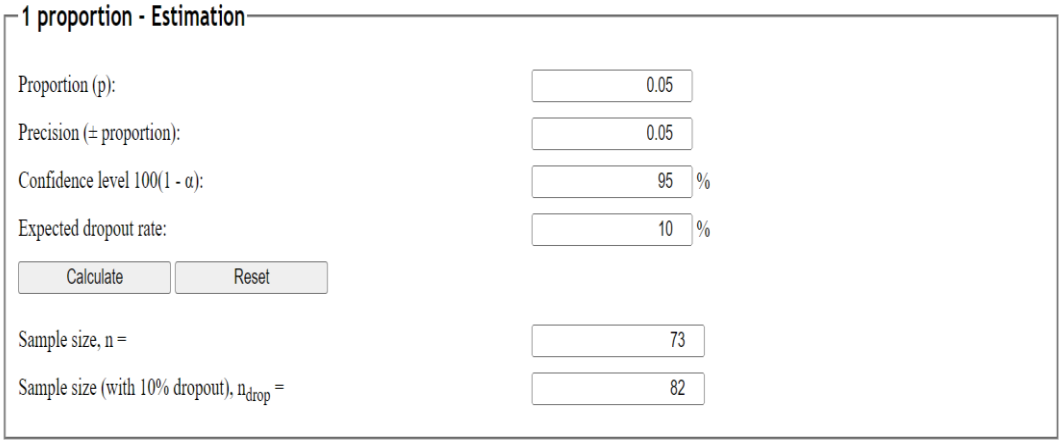
I. Reference population: Patient on warfarin treatment in Kelantan.

II. Source Population: Patient on warfarin registered in Hospital USM.

III. Sampling frame: Patients on warfarin who attended the medical clinic for follow-up from 1st January 2017 until 31st December 2021 based on inclusion and exclusion.

3.4 Sample Size Calculation

1. Objective no 1: To determine the proportion of GIB among patients on warfarin in Hospital USM. The sample size was calculated using a single proportion utilizing the software by Arifin 2017 and utilizing the following parameters:



Based on a study by (Beltrame et al., 2017), the overall incidence of major bleeding was 5.7%, which represents 6.3 major bleedings/100-patients-year, and it was higher among high-risk HAS-BLED score patients than in low-risk patients. The total number of subjects for the sample size was 82.

2. Objective no 2: To evaluate the association of high HASBLEED score ≥3 with GIB in Hospital USM. The sample size was calculated using Open Epi software Version 3 and utilizing the following parameters.

Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials	
Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	4
Percent of Unexposed with Outcome:	5
Percent of Exposed with Outcome:	23
Odds Ratio:	5.8
Risk/Prevalence Ratio:	4.7
Risk/Prevalence difference:	18

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	23	29	36
Sample Size-Nonexposed	92	115	141
Total sample size:	115	144	177

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction

Based on (Nantsupawat et al., 2018), in a retrospective cohort study of patients with atrial fibrillation, HAS-BLED score ≥3 and prior history of GIB within one year are independent risk factors for GIB among dabigatran users with an odds ratio of 5.85 (95% CI, 1.31-26.15; P = .021). The total number of subjects for the sample size was 115.

3. Objective 3: To identify significant risk factors associated with GIB among patients on warfarin in Hospital USM. The sample size was calculated using Open Epi software Version 3 and utilizing the following parameters.

Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials	
Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	80
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	5
Percent of Exposed with Outcome:	28
Odds Ratio:	7.5
Risk/Prevalence Ratio:	5.7
Risk/Prevalence difference:	23

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	41	39	48
Sample Size-Nonexposed	41	39	48
Total sample size:	82	78	96

References

Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction

Based on (Pisters et al., 2010), prior major bleeding is the most significant clinical risk factor for major bleeding within one year in patients with atrial fibrillation, with an odds ratio of 7.51 ($p<0.001$). The total number of subjects for the sample size was 82.

The highest sample size required for objective 2 was 115 and considered 20% of drop out, about 23. Thus, the final sample size needed for my study was 138.

3.5 Sampling Method

Convenience sampling was applied. A retrospective cohort study was conducted on patients 18 years old and above who were on warfarin for all indications attending the medical clinic Hospital USM follow-up was screened using inclusion and exclusion criteria. All eligible patients were included in the study.

3.6 Subject Criteria

Inclusion Criteria:

1. Age of 18 years old and above.

2. Started on warfarin from 1st January 2017 until 31st December 2021 under Hospital USM follow-up.

3. Using warfarin for all indications, including atrial fibrillation, prosthetic valve replacement, venous thromboembolism, left ventricle thrombus or arterial thrombosis and others.

Exclusion criteria:

1. Underlying genetic bleeding disorder.

2. Patients who developed GIB while on other types of anticoagulants such as direct oral anticoagulants.

3. Patients who had a history of GIB and recurrent episodes of GIB before 2017.

3.7 Research Tools and Variables

1. Renal function test, liver function test, haemoglobin level and international normalized ratio were obtained from LIS RESULT® application version 6.6.

2. HAS-BLED score was calculated using MD online calculator from the web https://www.mdcalc.com/calc/807/has-bled-score-major-bleeding-risk.
Other parameters required, such as uncontrolled hypertension, history of stroke, history of bleeding tendency and list of medications, were obtained from the patient's medical records.

3. The time in therapeutic range (TTR) score was calculated manually using the traditional formula: the number of visits with INR in range divided by the total number of visits, and the result was reported as a percentage. The estimated TTR required to achieve a benefit from warfarin treatment is $\geq 60\%$.

3. Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 27, SPSS Inc., Chicago, IL, USA) was used for data analysis.

3.8 Operational Definition

1. GIB is defined as any gastrointestinal bleeding either diagnosed based on clinical or endoscopic findings:

(1) Clinical hematemesis, melena, or haematochezia or positive stool occult blood.
(2) Needs of transfusion of two or more units of packed red blood cells or decline in Hb level of 2 g/dL or greater, or a systolic blood pressure <100 mmHg in patients negative for evident signs of GIB or occult blood test (Chen et al., 2014).
(3) Upper GI bleeding includes a haemorrhage originating from the oesophagus to the ligament of Treitz, which is at the duodenojejunal flexure. Lower GIB is bleeding that originates from a site distal to the ligament of Treitz (Kim, 2014).

Based on endoscopic findings, the most common cause of GIB is gastric and duodenal peptic ulcers, followed by esophagitis, gastritis, gastric erosion and duodenitis. Other reasons like malignancy or Mallory–Weiss syndrome (Oakland, 2019).

GIB events were further classified based on the Bleeding Academic Research Consortium (BARC) into type 2 or 3a. BARC type 2 is defined as any overt, actionable sign of haemorrhage that requires non-surgical medical intervention, hospitalization, or an increased level of care and prompts evaluation. BARC type 3a is defined as overt bleeding with a haemoglobin drop of 3 to 5 g/dL or any blood transfusion with overt bleeding (Mehran et al., 2011).

2. Patient on warfarin is defined as one who was started on warfarin as the first prescription vitamin K antagonist oral anticoagulant.

3. HAS-BLED SCORE consisted of uncontrolled hypertension, SBP >160 mmHg, abnormal renal and/or hepatic function, dialysis, transplant, serum creatinine >200 mmol/L, cirrhosis, bilirubin ≥ 2 upper limit of normal, AST/ALT/ALP ≥ upper limit of normal, previous ischaemic or haemorrhagic stroke, previous major haemorrhage or anaemia or severe thrombocytopenia, TTR <60% in the patient receiving VKA, aged >65 years or extreme frailty and concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs (NSAID) and or excessive alcohol per week. HAS-BLED score can be divided into non-high risk (HAS-BLED score ≤2) and high risk (HAS-BLED score ≥ 3). Based on 2020 European Society of Cardiology guidelines for diagnosing and managing atrial fibrillation, the HAS-BLED score should be considered to help address the modifiable bleeding risk factors and to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow up (Hindricks et al., 2021).

3.9 Data Collection

This is a retrospective cohort study that was conducted in Hospital USM, Kubang Kerian, Kelantan, Malaysia, from August 2022 to December 2022. Data were collected from 1st January 2017 to 31st December 2021 from electronic medical records of all patients with warfarin prescriptions. 488 warfarin anticoagulated patients were identified and enrolled on the pharmacy supply database. This study obtained approval from the Human Research Ethics Committee of USM (USM/JEPeM/22020140). The sample size was calculated using a sample size calculator by Arifin 2017 and open epi version 3.01 software. Data from patients aged 18 and above who had been initiated with warfarin for all indications from 2017 until 2021 were collected for this study. These patients were identified based on the clinic medical folder of Hospital USM. Using convenience sampling, 138 patients who fulfilled the inclusion and exclusion criteria were enrolled in this study. The risk of GIB was determined based on data from office records.

The data considered were age, race, sex, and parameters in HAS-BLED score such as renal function, liver function, INR, haemoglobin level and stool occult blood. This information was retrieved from LIS RESULT® application version 6.6. The HAS-BLED score was calculated using MD online calculator. Other required parameters such as uncontrolled hypertension, history of stroke, history of bleeding tendency and list of medications were obtained from the patient's medical records.

Based on the HAS-BLED score risk assessment, the patients were categorized as either low risk (HAS-BLED score ≤ 2) or high risk (HAS-BLED score ≥ 3). The occurrence of GIB was identified based on documented clinical or endoscopic findings. GIB events were further classified based on the Bleeding Academic Research Consortium (BARC) into type 2 or 3a.

HAS-BLED score assigns 0 to 9 points, including clinical and laboratory parameters: uncontrolled hypertension (+ 1 point), abnormal renal function (+1 point), abnormal liver function (+1 point), previous ischaemic or haemorrhagic stroke (+ 1 point), previous major haemorrhage or predisposition to bleeding (+1point), labile INR (+1 point), aged >65 years (+1 point), concomitant use of antiplatelet or NSAID (+1 point) or excessive alcohol per week (+1 point). The cumulative incidence of GIB was calculated from the date of warfarin initiation to the date of GIB event occurrence. All the data was recorded in the data collection sheet.

3.10 Statistical Analysis

All data were analysed using Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 27, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarise the socio-demographic and clinical characteristics and proportion of GIB among patients who received warfarin. Categorical data will be presented as frequency (n) and percentage (%). The evaluation of the associated and significant risk factors associated with GIB was analysed using simple and multiple logistic regression.