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# A Retrospective Study on the Association of Has-Bled Score with Risk of Gastrointestinal Bleeding Among Patients on Warfarin in Hospital Pakar Universiti Sains Malaysia

***Abstract –*** Warfarin is widely used in developing countries because of its low cost and availability compared to other novel oral anticoagulants. Early prevention of anticoagulant complications such as major bleeding, particularly gastrointestinal bleeding (GIB), is essential. In Malaysia, sufficient data on the occurrence and risk factors of GIB in individuals receiving warfarin are lacking. Objectives: To evaluate the efficacy of the HAS-BLED score in prognosticating GIB events in patients who underwent warfarin therapy at Hospital USM. Methodology: In this retrospective study, patients receiving warfarin at Hospital USM between January 2017 and December 2021 were categorised as high-risk (HAS-BLED score ≥ 3) or non-high-risk (HAS-BLED score ≤ 2) based on their medical data. The association between the HAS-BLED score and the occurrence of GIB was determined using simple logistic regression. Results: Data on 138 individuals were gathered, and 25 patients (18.1%) were found to have experienced GIB. The number of patients who had a GIB event during or after six months of warfarin therapy was 16 and 9, respectively. Of the high-risk group, 24 patients (96.0%) had experienced GIB, while only one non-high-risk group member had experienced a GIB event. The results of this study suggest a significant association between HAS-BLED score and GIB events (P<0.005). Conclusion: This novel bleeding risk score adequately stratifies GIB risk and predicts GIB events among patients who have received warfarin. In this study, inclusion in the high-risk group was associated with increased GIB events.

***Keywords –*** *Gastrointestinal bleeding, warfarin, HAS-BLED*

## 1. INTRODUCTION

Anticoagulant use continuously increases worldwide, partly attributed to the rise in stroke and thromboembolism. Among the commonly employed oral anticoagulants is warfarin, which acts as a vitamin K antagonist. It was the initial oral anticoagulant in use before introducing newer alternatives to the market.

In many developing countries, such as Malaysia, warfarin remains widespread due to cost limitations and availability [1]. Before prescribing warfarin, it is essential to conduct a thorough assessment to discern which patients are at high or low risk of experiencing bleeding complications. gastrointestinal bleeding (GIB) is a fatal anticoagulant complication that requires hospital admission and is a leading cause of mortality. The incidence of acute upper gastrointestinal bleeding (UGIB) reported in the United Kingdom is 103/100,000 adults per year, increasing with age [2]. Conversely, there is a lack of information about the incidence of GIB in Malaysia.

The HAS-BLED score was initially established to assess the one-year risk of major bleeding in atrial fibrillation patients undergoing warfarin treatment. It evaluates the clinical risk factors such as hypertension, abnormal renal/liver function, stroke, a history of bleeding tendency, labile International Normalized Ratio (INR), elderly patients > 65 years, and drug or alcohol use. Analysis of a real-world population of the Euro Heart Survey on atrial fibrillation revealed four independent risk factors of major bleeding within one year: prior major bleeding, age >65 years, clopidogrel use and kidney failure [3]. However, there is limited data available for HAS-BLED validation from Asia Cohorts and most of the data for HAS-BLED validation was done in several population cohorts, mainly from Europe [4].

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 [5].

By identifying the reversible risk factors contributing to significant bleeding, clinicians can implement preventive measures by modifying the risk factors and closely monitoring the INR value to achieve therapeutic levels. This identification is especially crucial in high-risk groups and can prevent the need to stop anticoagulant therapy. Moreover, the HAS-BLED score can guide clinicians to discuss with patients their bleeding risk with anticoagulants objectively and empower them to make an informed decision regarding initiating, continuing, or halting anticoagulant treatment if necessary. A high HAS-BLED score ≥3 indicates a higher likelihood of bleeding. The findings from this study may assist clinicians in allocating local healthcare resources towards safer anticoagulant options.

## 2. METHODOLOGY

### 2.1 Time and Location

This retrospective cohort study was conducted at Hospital Pakar Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia from August 2022 to December 2022. Data were collected from January 2017 to December 2021.

### 2.2 Methodology

This study obtained approval from the Human Research Ethics Committee of USM (USM/JEPeM/22020140).

A total of 138 patients out of 488 who met the inclusion criteria and were ≥18 years and on warfarin for any indication between 2017 and 2021 were enrolled in the study. Patients with underlying genetic bleeding disorder or patients who developed GIB while on other types of anticoagulants such as direct oral anticoagulants or patients who had a history of GIB and recurrent episodes of GIB before 2017 were excluded from this study. These patients were selected using convenience sampling.

The HAS-BLED score comprises nine points, incorporating clinical and laboratory parameters. These include uncontrolled hypertension with systolic blood pressure >160mmHg (+1 point), abnormal renal function with serum creatinine >200 mmol/L or dialysis or renal transplant (+1 point), abnormal liver function with liver cirrhosis or bilirubin ≥2 upper limits of normal, Alanine Transaminase (ALT) / Aspartate Transaminase (AST) /Alkaline Phosphatase (ALP) ≥3 upper limits of normal (+1 point), previous ischemic or haemorrhagic stroke (+1 point), bleeding tendency which requiring blood transfusion, hospitalisation and/or decrease in haemoglobin (Hb) level of 2 g/L (+1 point), labile International Normalized Ratio (INR) with Therapeutic Therapy Range (TTR) <60% (+1 point), age >65 years (+1 point), concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs (NSAID) (+1 point), or excessive alcohol consumption per week (+1 point) (Pisters et al. 2010).

The HAS-BLED score was calculated using the MD online calculator. Patient age, race, sex, and parameters in the HAS-BLED were obtained from the LIS RESULT® application version 6.6. Additional parameters such as uncontrolled hypertension, history of stroke, history of bleeding tendency and medication lists were extracted from the patient's medical records. 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 ≥ 60% [6].

GIB is defined as any bleeding in the gastrointestinal tract diagnosed based on clinical or endoscopic findings, including:

(1) Clinical signs such as hematemesis, melena, haematochezia, or positive stool occult blood.

(2) Transfusion ≥ 2 units of packed red blood cells or a decline in haemoglobin (Hb) level of 2 g/dL or greater, or a systolic blood pressure <100mmHg in patients without evident signs of GIB or positive occult blood test [7].

(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 [8].

The cumulative incidence of GIB was calculated from the date of warfarin initiation to the date of GIB event occurrence, which was identified based on clinical or endoscopic findings documented in the medical records. GIB events were further classified based on the Bleeding Academic Research Consortium (BARC) into type 2 or 3a. BARC type 2 is any overt, actionable sign of bleeding that requires non-surgical medical intervention, hospitalization, or increased care and prompts evaluation. BARC type 3a is overt bleeding with a haemoglobin drop of 3 to 5 g/dL or any blood transfusion with overt bleeding [9].

## 3. RESULT

The baseline demographic of 138 patients as detailed in Table 1.

Regarding bleeding events, 25 patients (18.1%) experienced GIB during the study period, with 16 patients (64%) experiencing GIB within six months and nine patients (36%) after six months of warfarin therapy (Figure 1).

13 of 25 GIB patients underwent esophagogastroduodenoscopy (OGDS), and the most common causes of GIB were Forrest III ulcer (20%) and gastritis esophagitis (20%) (Table 2).

Atrial fibrillation was the most common indication for warfarin use (50.7%), but there was no significant association between any indications and the development of GIB (Table 3).

A significant association was found between the HAS-BLED score and the occurrence of GIB ($P<0.001$), with 24 patients (96%) in the high-risk group developing GIB. In contrast, only one patient (4%) in the low-risk group experienced GIB (Table 4).

The association of HAS-BLED score components with GIB incidence is described in Table 5.

Simple logistic regression showed six significant risk factors of GIB identified in Table 6.

## 4. DISCUSSION

We analysed data for 138 out of 488 patients who received warfarin between January 2017 and December 2021 at Hospital USM. The Malay ethnic group remains the predominant Kelantan ethnicity accounting for 98.2%, followed by the Chinese, who comprised 7.2%. The study involved patients on warfarin therapy for various indications like atrial fibrillation, left ventricular clots, pulmonary embolism, post-valvular replacement, and deep vein thrombosis. Most GIB occurred in patients with atrial fibrillation (49.6%) and left ventricular clots (13.3%).

The findings propose the application of HAS-BLED scores to evaluate the risk of GIB in all indications. The validation of the HAS-BLED score has been extended to acute venous thromboembolism (VTE). In this context, patients with acute VTE and HAS-BLED scores ≥3 points are deemed to be at an elevated risk of experiencing significant bleeding [10].

The present study demonstrated that GIB has an overall incidence of 18.1% (25/138) and a 1-year incidence rate of 5.1%. The incidence of GIB in our study was higher than that reported in Taiwan, where 3.9% per patient-year incidence of GIB was observed with 36 out of 401 patients experiencing at least one episode of GIB [7]. The higher incidence of GIB in our study can be attributed to 18 out of 25 GIB events being recorded in individuals over 65 years. Of the 25 GIB patients, 13 underwent upper gastrointestinal endoscopy. The causes of GIB included Forrest III ulcer (5), gastritis esophagitis (5), gastric polys (1), duodenal polys (1) and Forrest II a (1). 17 GIB patients (12.3%) had type 2 BARC in this study. The BARC classification was chosen because it is hierarchically graded and based on consensus, which allows for comprehensive and consistent reporting [9].

A significant association was seen between the high-risk group and GIB among patients who received warfarin in Hospital USM ($P < 0.001$). Two patients (1.8%) in the high-risk group did not experience GIB, likely due to insignificant risk factors such as uncontrolled hypertension and medication use such as antiplatelets and NSAIDs. However, one patient (4%) in the low-risk group who used warfarin for valve replacement had GIB event. This was attributed to the patient's advanced age> 65 years, which was recognised as a noteworthy predisposing factor.

GIB incidence was found to be greater in patients aged 65 or older, with an odds ratio of 4.516 with confidence interval 95% and p value 0.002 his may be because warfarin metabolizes more slowly in older people, who are more likely to take medicines for multiple concomitant comorbidities, increasing the risk of drug interactions [7]. Of the patients with labile INR with TTR, <60% had a significantly higher GIB risk, with an odds ratio of 9.383, versus patients with stable INR TTR ≥60%. TTR reflects treatment efficacy and prevents further complications.

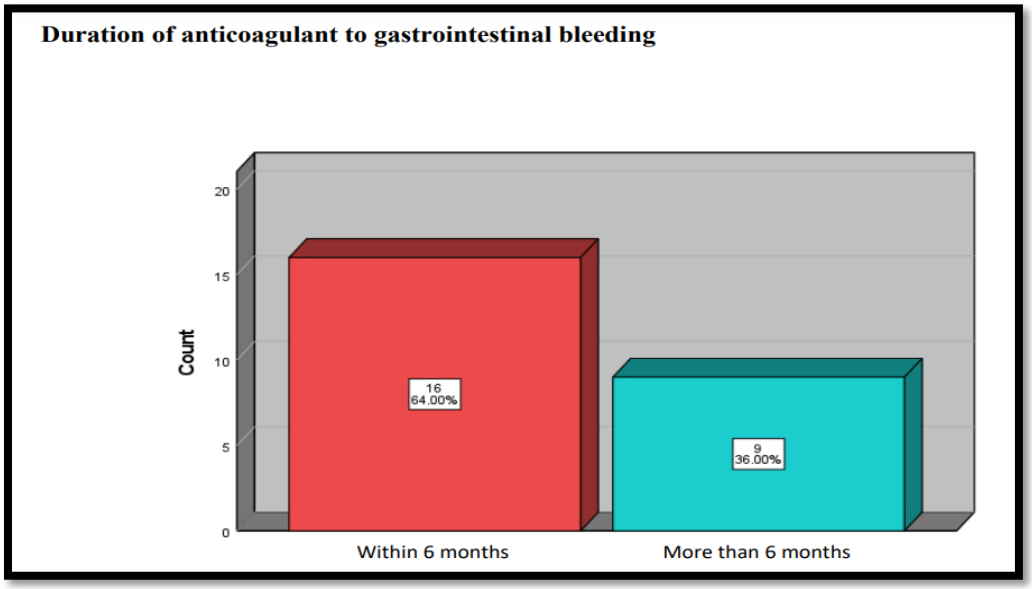


**Figure 1.** Duration of anticoagulant to gastrointestinal bleeding

**Table 1.** The sociodemographic characteristics

| Variables | n (%) |
|---|---|
| Age | |
| <65 years old | 79(57.2) |
| ≥65 years old | 59(42.8) |
| Gender | |
| Male | 80(58.0) |
| Female | 58(42.0) |
| Ethnicity | |
| Malay | 128(92.8) |
| Chinese | 10(7.2) |
| Indian | 0(0.0) |
| Others | 0(0.0) |
| HASBLED | |
| Low risk ≤ 2 | 112(81.2) |
| High risk ≥3 | 26(18.8) |

**Table 2.** OGDS findings

| Source of bleeding | Patients (n) (%) |
|---|---|
| Upper GIB | |
| Forrest III ulcer | (5) 20 |
| Gastritis esophagitis | (5) 20 |
| Gastric polys | (1) 4.0 |
| Duodenal polys | (1) 4.0 |
| Forrest II a | (1) 4.0 |
| No identifiable source | (12) 48 |

**Table 3.** The indication of warfarin with the presence of GIB

| Indication of warfarin | Gastrointestinal bleeding | | Total n (%) | *P*-value |
|---|---|---|---|---|
| | Yes n (%) | No n (%) | | |
| DVT | 16(4.2) | 3(12.0) | 19(13.8) | >0.95[b] |
| Pulmonary embolism | 10(8.8) | 2(8.0) | 12(8.7) | >0.95[b] |
| Valvular replacement | 6(5.3) | 1(4.0) | 7(5.1) | >0.95[b] |
| LV clot | 15(13.3) | 4(16.0) | 19(13.8) | 0.750[b] |
| Atrial fibrillation | 56(49.6) | 14(56.0) | 70(50.7) | 0.560[a] |
| Others | 10(8.8) | 1(4.0) | 11(8.0) | 0.689[b] |

[a]Pearson chi-sqaure test applied; less than 20% expected count <5
[b]Fisher exact test applied; more than 20% expected count <5

**Table 4.** The distribution of GIB events according to HAS-BLED score risk group

| HAS-BLED score | Gastrointestinal bleeding | | Total n (%) | *P*-value[a] |
|---|---|---|---|---|
| | Yes n (%) | No n (%) | | |
| Low risk (≤2 ) | 1(4.0) | 111(98.2) | 112(81.2) | <0.001 |
| High risk (≥3) | 24(96.0) | 2(1.8) | 26(18.8) | |

[a]Fisher exact test applied; more than 20% of expected count <5

**Table 5.** The descriptive statistics of HAS-BLED component and GIB

| HAS-BLED component | Gastrointestinal bleeding | | Total n (%) | *P*-value |
|---|---|---|---|---|
| | No n (%) | Yes n (%) | | |
| Uncontrolled hypertension | | | | |
| No | 90(79.6) | 21(84.0) | 111(80.4) | 0.784[b] |
| Yes | 23(20.4) | 4(16.0) | 27(19.6) | |
| Abnormal renal function | | | | |
| No | 105(92.9) | 16(64.0) | 121(87.7) | <0.001[b] |
| Yes | 8(7.1) | 9(36.0) | 17(12.3) | |
| Abnormal liver function | | | | |
| No | 110(97.3) | 21(84.0) | 131(94.9) | 0.020[b] |
| Yes | 3(2.7) | 4(16.0) | 7(5.1) | |
| Stroke | | | | |
| No | 103(91.2) | 16(64.0) | 119(86.2) | <0.001[b] |
| Yes | 10(8.8) | 9(36.0) | 19(13.8) | |
| Bleeding tendency | | | | |
| No | 110(97.3) | 19(76.0) | 129(93.5) | <0.001[b] |
| Yes | 3(2.7) | 6(24.0) | 9(6.5) | |

| | | | | |
|---|---|---|---|---|
| Labile INR | 95(84.1) | 9(36.0) | 104(75.4) | <0.001[a] |
| No | 18(15.9) | 16(64.0) | 34(24.6) | |
| Yes | | | | |
| Age | | | | |
| <65 years old | 72(63.7) | 7(28.0) | 79(57.2) | 0.001[a] |
| ≥65 years old | 41(36.3) | 18(72.0) | 59(42.8) | |
| Drugs(antiplatelet/alcohol) | | | | |
| No | 104(92.0) | 21(84.0) | 125(90.6) | 0.253[b] |
| Yes | 9(8.0) | 4(16.0) | 13(9.4) | |

[a]Pearson chi-square applied; <20% expected count less than 5
[b]Fisher exact test applied; >20% expected count less than 5

**Table 6.** Associated factors of GIB

| **Variables** | **b** | **Crude OR (95% CI)** | **Wald statistics** | ***P*-value** |
|---|---|---|---|---|
| Uncontrolled hypertension | | | | |
| No | 0 | 1 | | |
| Yes | -0.294 | 0.745(0.233, 2.385) | 0.245 | 0.620 |
| Abnormal renal function | | | | |
| No | 0 | 1 | | |
| Yes | 1.999 | 7.383(2.487, 21.914) | 12.970 | <0.001 |
| Abnormal liver function | | | | |
| No | 0 | 1 | | |
| Yes | 1.944 | 6.984(1.456, 33.504) | 5.902 | 0.015 |
| Stroke | | | | |
| No | 0 | 1 | | |
| Yes | 1.757 | 5.794(2.041, 16.445) | 10.893 | 0.001 |
| Bleeding tendency | | | | |
| No | 0 | 1 | | |
| Yes | 2.449 | 11.579(2.665, 50.307) | 10.679 | 0.001 |
| Labile INR | | | | |
| No | 0 | 1 | | |
| Yes | 2.239 | 9.383(3.594, 24.494) | 20.912 | <0.001 |
| Age | | | | |
| <65 years old | 0 | 1 | | |
| ≥65 years old | 1.508 | 4.516(1.740, 11.718) | 9.602 | 0.002 |
| Drugs(antiplatelet/alcohol) | | | | |
| No | 0 | 1 | | |
| Yes | 0.789 | 2.201(0.620, 7.820) | 1.488 | 0.223 |

OR – Odds ratio CI – Confidence interval

Abnormal renal function, as opposed to normal renal function, was found to significantly increase bleeding risk, with an odds ratio of 7.383. As demonstrated in a study conducted on a Chinese population with atrial fibrillation [11], renal failure while on dialysis is associated with GIB. Patients who experience a decline in renal function coupled with the buildup of uremic toxins are more susceptible to an elevated risk of bleeding due to platelet recruitment and activation abnormalities [12]. Therefore, close monitoring is required when patients with declining renal function are prescribed warfarin.

The study also found that patients with abnormal liver function had a 31.42% higher GIB risk, with an odds ratio of 6.984. Warfarin impacts hepatic metabolism, which affects the coagulation factors involved in bleeding. Patients with a tendency to bleed had an 11.579 times greater GIB risk than those without a tendency to bleed. Similarly, a history of GIB has been identified as an independent GIB risk factor among warfarin users [13]. Finally, patients with a history of stroke were found to have a significantly increased GIB risk compared to those without a history of stroke, with an odds ratio of 5.794. Thus, maintaining a balance between the advantages of preventing strokes and the potential risk of bleeding is vital when administering oral anticoagulants.

Applying the HAS-BLED score is crucial for various oral anticoagulants with respective indications. However, evaluating novel oral anticoagulants in replacing warfarin for high-risk patients is vital due to their lower bleeding effects, even though a dose adjustment is needed for impaired kidney function [14].

Our study had a few limitations that need to be acknowledged. First, we collected data retrospectively, and the HAS-BLED score was not routinely assessed and documented before initiating anticoagulation except in patients with very high bleeding risk. This may have led to a bias in selecting patients for anticoagulation.

Second, we do not have data on a few confounding factors that can affect the GIB event such as platelet and haemoglobin level patients prior to warfarin initiation and concomitant drugs used or dietary intake that can interact with warfarin and lead to GIB. Finally, our study had a smaller sample size than previous studies, and the study duration was shorter than that of more extensive studies.

For the future recommendation, this study has demonstrated that warfarin is potentially dangerous for patients with a HAS-BLED score ≥ 3 and is not absolutely contraindicated. However, in countries like Malaysia, where cost may be a concern, warfarin can still be considered for patients with a low HAS-BLED score ≤2 and a low risk of bleeding. With the availability of novel oral anticoagulants, high-risk bleeding patients should be prescribed with NOACs if they are affordable, with an adjustment dose if needed. Warfarin should only be used for specific indications such as prosthetic valve replacement and antiphospholipid syndrome.

A prospective study with proper follow-up may provide a more accurate representation of the real-world application of the HAS-BLED score in anticoagulated patients on warfarin. Future studies on this topic should continue to promote using the HAS-BLED score as a bleeding risk assessment tool before commencing any anticoagulant therapy.

## 5. CONCLUSION

The present study exhibited a significant association between HAS-BLED score and GIB. Elevated HAS-BLED score (≥ 3) was observed to be linked with increased GIB events. Therefore, HAS-BLED score is an essential bleeding risk assessment tool before initiating anticoagulant treatment and optimising the identified risk factors through proper monitoring, particularly for those at high risk of bleeding.

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