

ORIGINAL ARTICLE

Analysis of Risk Factors for Bleeding in Patients with Cardiovascular Disease Undergoing Warfarin Treatment at Rsud Kabupaten Tangerang

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ABSTRACT

Bleeding complications are a major contributor to hospitalization among cardiovascular patients on warfarin therapy, yet the causative factors remain incompletely characterized. This retrospective case-control study aimed to identify significant risk factors and their potential interaction in bleeding incidence among cardiovascular disease (CVD) patients at RSUD Kabupaten Tangerang. Medical-record data from CVD patients on warfarin hospitalized with or without bleeding between January 2023 and December 2024 were analyzed using JAMOMI, encompassing bivariate, multivariate, and interaction analyses. A total of 132 patients were enrolled, comprising 44 (33.3%) cases with bleeding and 88 (66.7%) controls without bleeding. Fisher's exact test, employed due to sparse and unbalanced data, identified significant associations with herb use ($p < 0.001$, OR=460), INR ≥ 3 ($p < 0.001$, OR=8.33), and hypofibrinogenemia ($p < 0.001$, OR=179). Firth's penalized logistic regression confirmed herb use (aOR=25.33, $p < 0.001$) and hypofibrinogenemia (aOR=19.10, $p < 0.001$) as independently and strongly associated with bleeding, with a strong model fit (Nagelkerke $R^2 = 0.854$). However, the likelihood ratio test for the synergistic interaction between these two factors was not statistically significant ($\chi^2 = 2.78$, $p = 0.095$). Overall, herb use and hypofibrinogenemia are independently risk factors for bleeding in warfarin-treated cardiovascular patients; the interaction between them was not statistically significant, so clinicians should screen for herb use and monitor fibrinogen levels.

Keywords: Cardiovascular, Herb Use, Hypofibrinogenemia, Risk Factors, Warfarin.

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Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide and represents a major public health challenge. According to global estimates, approximately 18.5 million deaths were attributed to CVD in 2019, and the burden is expected to continue increasing in the coming years [1]. In Indonesia, the prevalence of heart disease was reported as 0.85% of the total population in the 2023 National Health Survey [2].

Patients with conditions such as atrial fibrillation and valvular heart disease frequently require long-term anticoagulation therapy to prevent thromboembolic complications [3,4]. Warfarin remains one of the most widely prescribed oral anticoagulants for these indications, exerting its effect by inhibiting vitamin K epoxide reductase and thereby reducing the synthesis of coagulation factors II, VII, IX, and X, as well as proteins C and S [5].

Despite its clinical benefits, warfarin carries a substantial risk of bleeding influenced by multiple patient (age and gender) and treatment-related factors (INR, duration, weekly dose), including drug interactions and coagulation abnormalities. In Indonesia

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herbal medicine use has shown an increasing trend [6–8], raising concerns regarding potential herb–warfarin pharmacokinetic and pharmacodynamic interactions that may potentiate bleeding risk [6,9,10].

Fibrinogen is essential for fibrin clot formation; hypofibrinogenemia may therefore increase bleeding risk by impairing haemostasis. Emerging evidence suggests that fibrinogen assessment provides clinically relevant information beyond conventional INR monitoring in warfarin-treated patients [11–13].

Although bleeding risk factors in warfarin-treated patients have been widely studied, evidence regarding the specific roles of herb use and hypofibrinogenemia remains limited, particularly in Indonesia. Moreover, their potential interaction and combined effect on bleeding risk have not been well characterized. This study, therefore, investigated the independent and interactive associations of herb use and hypofibrinogenemia with bleeding in hospitalized cardiovascular patients receiving warfarin.

METHODS

Study Design and Data Resource

This retrospective case-control study used data from the electronic medical records (e-MR) of RSUD Kabupaten Tangerang, covering the period January 2023 to December 2024. Cases were defined as warfarin-treated cardiovascular patients hospitalized with bleeding events, while controls were warfarin-treated cardiovascular patients hospitalized during the same period without bleeding events. Patients discharged against medical advice or with incomplete medical records were excluded. Ethical approval was obtained from the Ethics Committee of the Faculty of Pharmacy, Universitas Pancasila (No. 239/KPEK-FFUP/II/2026).

Variables

Data extracted from e-MR included demographic characteristics (age, gender, smoking history) and clinical variables (duration of warfarin use, major drug interactions, herb use, INR, hypofibrinogenemia, and weekly warfarin dose). Age ≥ 60 years and weekly warfarin dose ≥ 23 mg were categorized according to thresholds reported in previous studies [14,15]. Major drug interactions were classified using the Medscape

Drug Interaction Checker. Hypofibrinogenemia was defined as a fibrinogen level < 200 mg/dL [16]. Information on herbal medicine use was obtained from physicians, nurses, and clinical pharmacists' documentation recorded in the Integrated Patient Progress Notes (IPPN).

Statistical analysis

Nine predefined demographic and clinical variables (age, Gender, smoking history, duration of warfarin use, major drug interactions, herb use, INR ≥ 3 , hypofibrinogenemia, and weekly warfarin dose) were summarized as frequencies and percentages. Bivariate associations between each variable and bleeding were assessed using the chi-square test. Because the frequency distribution for herb use and hypofibrinogenemia produced small expected cell counts (fewer than five in one cell), Fisher's exact test was used instead of the chi-square test for these two variables to ensure valid bivariate inference. Variables that reached statistical significance at the bivariate level ($p < 0.025$) were subsequently entered into a multivariable logistic regression model to identify factors independently associated with bleeding. Because herb use and hypofibrinogenemia produced markedly large odds ratios with wide confidence intervals, indicative of quasi-complete separation, both variables were reanalyzed at the bivariate and multivariable levels using Firth's penalized logistic regression to obtain bias-corrected effect estimates. To determine whether an interaction exists between herb use and hypofibrinogenemia, a multiplicative interaction term (herb use $\times$ hypofibrinogenemia) was incorporated into a binomial Generalized Linear Model with a logit link function. The statistical significance of this interaction term was subsequently evaluated using the likelihood ratio test (LRT). All analyses were performed using JAMOVI version 2.6.2, with Firth's regression implemented via the ClinicoPath module; a p -value < 0.05 was considered statistically significant.

Population and Samples

All eligible cardiovascular patients receiving warfarin therapy at Tangerang Regency General Hospital between January 2023 and December 2024 were included. A total sampling method was employed using

Table 1. Odds Ratio from Previous Studies Used for Sample Size Estimation

No	Risk Factors	Odds ratio (OR)	Prevalence (%)
1	Smoking History	2.89	22.8
2	Food History (Vegetable Consumption)	2.99	35.4

secondary data from electronic medical records (e-MR). Since sample sizes for odds ratios specific to herb use and hypofibrinogenemia in warfarin-treated cardiovascular populations were not available in the literature at the time of protocol development, sample size estimation was instead based on odds ratios for smoking history and vegetable consumption reported in comparable studies (Table 1) [14,17]. with the largest and most conservative estimate selected.

Hipotesis Test Formula K control per case [18]

$$n = \frac{(Z_{1-\alpha} \sqrt{(1+1/k)x(Px(1-P))} + (Z_{1-\beta} \sqrt{(P_1(1-P_1) + (P_2x(1-P_2))/k}))^2}{(P_1 - P_2)^2}$$

$$P_1 = \frac{(OR) \times P_2}{((OR) \times P_2) + (1 - P_2)}$$

Information:

P_1 = Proportion of subjects exposed to case group

P_2 =

Proportion of subject expose to the control group

OR = Odd Ratio

K = Comparison of cases and controls

$$P = \frac{(P_1 + kP_2)}{(1 + K)}$$

Correction factor if very few cases exist

$$n = \frac{r+1}{2 \times r} \times \frac{2(Z_{1-\alpha} + Z_{1-\beta})^2 \times P(1-P)}{(P_0 - P_1)^2}$$

$$p = \frac{(r \times P_0) + P_1}{r + 1}$$

Information:

r = comparison of case and controls

$$P_2 = P_0 =$$

Propotion of subject expose to the control group

We used a 1:2 comparison ratio because the number of cases of concern was small, given the low incidence of bleeding in patients with cardiovascular disease receiving warfarin therapy.

Sample size estimation was based on the odds ratio for dietary history (vegetable consumption) reported in

a previous study (OR = 2.99; prevalence = 35.4%; Table 1). This variable was chosen because its relatively high prevalence generated the largest and most conservative sample size requirement. Using a 1:2 case-to-control ratio, a 95% confidence level, and 80% power, the minimum sample size was estimated at 40 cases and 80 controls. Allowing for a 10% dropout rate, the final required sample comprised 44 cases and 88 controls.

RESULT AND DISCUSSION

A total of 132 hospitalized cardiovascular patients receiving warfarin therapy were included, comprising 44 patients with bleeding (33.3%) and 88 without bleeding (66.7%). Baseline demographic and clinical characteristics are presented in Table 2 and Figure 1.

Demographic characteristics

Three demographic factors were evaluated: age, sex, and smoking history. Patients aged ≥ 60 years accounted for 46 (34.8%), of whom 10 (7.6%) experienced bleeding, and 36 (27.3%) did not. Among the 86 patients aged < 60 years (65.2%), 34 (25.8%) had bleeding, and 52 (39.4%) did not. Females represented a larger proportion of the population ($n = 73$, 55.3%), with 28 (21.2%) experiencing bleeding compared with 45 (34.1%) not experiencing bleeding. Among 59 male patients (44.7%), 16 (12.1%) had bleeding, and 43 (32.6%) did not. Regarding smoking history, 51 patients (38.6%) had smoked; bleeding occurred in 21 (15.9%) compared with 30 (22.7%) who did not bleed. Among 81 never-smokers (61.4%), 23 (17.4%) experienced bleeding versus 58 (43.9%).

Clinical characteristics

The independent variables analyzed in this study included duration of warfarin use, weekly warfarin dose, INR, hypofibrinogenemia, major drug interactions, and herb use. Additional data on patients' history of herb use and the clinical indications for warfarin therapy were also collected.

Regarding the duration of warfarin therapy, 99 patients (75.0%) had received warfarin for ≥ 1 year; of these, 36 (27.3%) experienced bleeding, and 63 (47.7%) did not. In contrast, 33 patients (25.0%) had received

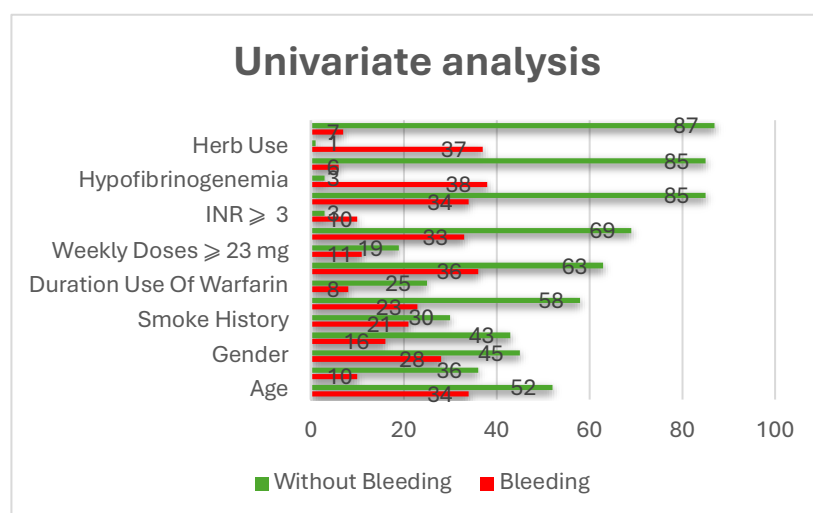


Figure 1. Risk Factors for Bleeding in Warfarin-Treated Patients

warfarin for <1 year, including 8 (6.1%) with bleeding events and 25 (18.9%) without bleeding.

For the weekly warfarin dose, 30 patients (22.7%) received ≥ 23 mg/week; 11 (8.3%) experienced bleeding, and 19 (14.4%) did not. Meanwhile, 102 patients (77.3%) received <23 mg/week; among them, 33 (25.0%) experienced bleeding and 69 (52.3%) did not.

With respect to anticoagulation status, 13 patients (9.8%) had an INR ≥ 3.0 , including 10 (7.6%) who experienced bleeding and 3 (2.3%) who did not. Conversely, 119 patients (90.2%) had an INR <3.0, of whom 34 (25.8%) experienced bleeding, and 85 (64.4%) did not. Hypofibrinogenemia was observed in 41 patients (31.1%), with bleeding occurring in 38 patients (28.8%) and no bleeding in 3 patients (2.3%). In comparison, 91 patients (68.9%) had normal fibrinogen levels, among whom 6 (4.5%) experienced bleeding, and 85 (64.4%) did not.

Major drug interactions involving warfarin were identified in 31 patients (23.5%), including 9 patients (6.8%) with bleeding events and 22 patients (16.7%) without bleeding. In contrast, 101 patients (76.5%) had no major drug interactions, of whom 35 (26.51%) experienced bleeding and 66 (49.99%) did not. Herb use was reported in 38 patients (28.8%). Among these patients, 37 (28.0%) experienced bleeding, whereas only 1 patient (0.8%) did not. Conversely, 94 patients (71.2%) had no history of herb use; among them, 7 patients (5.3%) experienced bleeding and 87 patients (65.9%) did not.

ANALYSES

Bivariate

Bivariate analysis identified three factors significantly associated with bleeding; these associations have also been reported in a companion analysis of the data set [19] and are presented here only as the basis for the multivariate model below. The extremely large ORs for herb use and hypofibrinogenemia signaled quasi-complete separation (37 of 38 Herb Users experienced bleeding), so Firth's penalized logistic

regression applied, yielding bias-corrected estimates for herb use (291.66; 95% CI: 47.48–1791.84; $p < 0.001$) and hypofibrinogenemia (144.69; 95% CI: 36.87–567.88; $p < 0.001$) (Table 3). Both associations remained statistically significant after correction, although the wide confidence intervals reflect residual impression from sparse data in the non-bleeding stratum.

Multivariate

Multivariable logistic regression with Firth's correction identified herb use (aOR = 25.33, 95% CI: 3.60–185.42; $p < 0.001$) and hypofibrinogenemia (aOR = 19.10, 95% CI: 3.19–114.29; $p < 0.001$) as the strongest independent association of bleeding (Table 3). INR ≥ 3 was no longer statistically significant after adjustment (aOR = 3.69, 95% CI: 0.33–41.30; $p = 0.321$), but was retained in the final model because it met the pre-specified bivariate entry criterion ($p < 0.025$); it was not removed post hoc, since further variable elimination in a dataset already affected by quasi-complete separation risk destabilizing the remaining estimates. The model demonstrated strong explanatory power (Nagelkerke $R^2 = 0.854$), and the reduction in effect estimates after penalization is consistent with genuine associations of herb use and hypofibrinogenemia rather than a pure artefact of separation.

Table 2. Patients Demographic and Clinical Characteristics (n=132)

Patient Characteristic	Frequency (n)	Percentage (%)
Bleeding		
Bleeding	44	33.3
Without Bleeding	88	66.7
Age		
≥ 60 years	46	34.8
< 60 years	86	65.2
Gender		
Female	73	55.3
Male	59	44.7
Smoking History		
No Smoking	81	61.4
Smoking	51	38.6
Duration of warfarin use		
≥ 1 year	99	75
< 1 year	33	25
Major drug interactions		
No	101	76.5
Yes	31	23.5
Herb Use		
No	94	71.2
Yes	38	28.8
INR ≥ 3		
Yes	13	9.8
No	119	90.2
Hypofibrinogenemia		
Yes	41	31.1
No	91	68.9
Weekly dose ≥ 23 mg		
Yes	30	22.7
No	102	77.3
Herb Use		
Garlic	11	28.9
Ginger Herb	9	23.7
Turmeric Herb	8	21.1
Combination 3 (Garlic, Ginger, Tumeric)	4	10.6
Combination 2 (Ginger & Tumeric)	2	5.2
Green Tea	2	5.2
Other (Mango and Tape)	2	5.2

Demographic and Clinical Factors Not Associated with Bleeding

Age, sex, smoking history, duration of warfarin use, major drug interactions, and weekly warfarin dose

were not independently associated with bleeding after multivariate adjustment. The absence of a sex effect is consistent with previous findings in warfarin-treated populations [14]. The non-significant association with

smoking may reflect CYP1A2 induction by smoking, which accelerates warfarin metabolism and reduces anticoagulant exposure [9,20], an effect documented in Southeast Asian populations [21]. Major drug interactions, higher warfarin doses, and longer treatment duration have been linked to bleeding in other studies [9,22]. but their effects were attenuated in the present analysis, likely because of the dominant influence of herb use and hypofibrinogenemia. Although $\text{INR} \geq 3$ was associated with bleeding in the bivariate analysis (Table 3), the loss of significance after adjustment suggests that INR alone inadequately captures the full spectrum of homeostatic risk in this cohort [23].

Herb Use as a Predominant Risk Factor for Bleeding

Herb use emerged as the factor most strongly and independently associated with bleeding (Table 3). Given the increasing prevalence of herbal medicine use in Indonesia, rising from 49.53% in 2010 to 62.3% in 2021 [6–8], concomitant herb–warfarin use represents an important but underrecognized contributor to bleeding risk. In this cohort, the most frequently used herbs were garlic (*Allium sativum*, 28.95%), ginger (*Zingiber officinale*, 23.68%), and turmeric (*Curcuma longa*, 21.05%) (Table 2), each possessing pharmacologically active constituents capable of potentiating warfarin's anticoagulant effects through distinct and overlapping mechanisms.

Garlic contains S-allylmercaptocysteine (SAMC), a compound demonstrated *in silico* to inhibit CYP3A4, an enzyme responsible for the biotransformation of R-warfarin, potentially elevating plasma warfarin concentrations and prolonging anticoagulation [24]. Additionally, garlic may impair platelet aggregation, further contributing to homeostatic dysfunction. Ginger contains flavonoids and terpenoids that interact with multiple CYP450 isoforms, including CYP1A2, 2C9, 2C19, 2D6, and 3A4/5, thereby prolonging warfarin metabolism and elevating INR. A clinically documented case reported supratherapeutic INR elevation exceeding 10 following sustained ginger ingestion in a 76-year-old patient receiving warfarin therapy [25]. Turmeric enhances warfarin's anticoagulant activity by simultaneously increasing prostaglandin PGI_2 synthesis,

reducing thromboxane A_2 (TXA_2) production, modulating cyclic adenosine monophosphate (cAMP) levels in platelets, and inhibiting CYP450 enzymes [25,26].

Patients may also perceive herbal products as safer than conventional medicines, and limited knowledge of warfarin therapy and herb–drug interactions may contribute to inappropriate concomitant use [27,28]. Previous studies have reported considerably smaller effect sizes for herb–warfarin interactions and bleeding risk (OR 1.08–3.40) [10,17,29–31]. compared with the adjusted OR of 25.33 observed in this study, likely reflecting differences in sample size, study design, and patterns of herb consumption, particularly the frequent use of garlic, ginger, and turmeric in this population.

Hypofibrinogenemia as an Independent

Hypofibrinogenemia remained independently associated with bleeding after Firth correction, whereas $\text{INR} \geq 3$ was no longer significant (Table 3). This finding suggests that fibrinogen status provides additional homeostatic information beyond conventional INR monitoring. Hypofibrinogenemia may arise from multiple mechanisms in warfarin-treated patients, including inherited fibrinogen disorders, hepatic dysfunction, disseminated intravascular coagulation (DIC), thrombolytic therapy, and long-term warfarin use, altering coagulation–fibrinolysis balance [11,32].

Warfarin-induced hypofibrinogenemia may occur through mechanisms beyond its inhibition of vitamin K-dependent clotting factors. Reduced thrombin generation impairs fibrin clot formation and decreases activation of Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), resulting in enhanced fibrinolysis and increased fibrinogen consumption. This process may contribute to hypofibrinogenemia and further increase bleeding susceptibility [13,33]. These pathways suggest that INR elevation does not fully capture fibrinogen-related homeostatic abnormalities, a finding corroborated by Hoppensteadt et al [34]. The proposed pathway is illustrated in Figure 2.

Interaction and Model Performance

The likelihood ratio test showed no significant interaction between herb use and hypofibrinogenemia ($\chi^2 = 2.78$, $\text{df} = 1$, $p = 0.095$); the interaction term was

Table 3. Bivariate and Multivariate Analyses

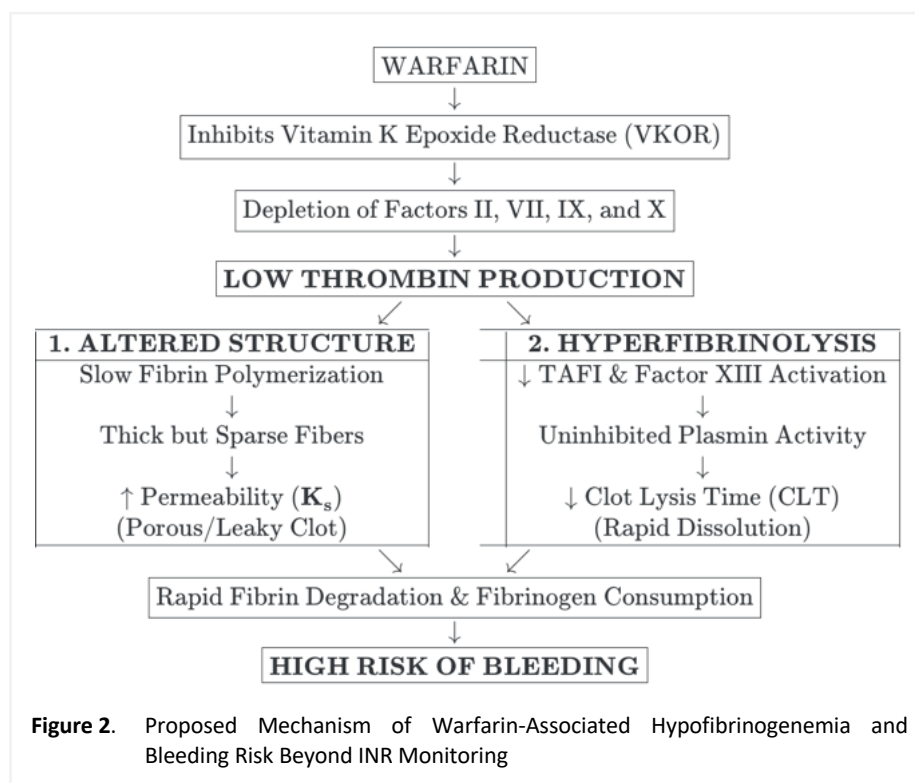
Category	Bivariate			Multivariate					
Factors	Odds ratio (95% CI)1	Crude Odds Ratio3 (95% CI)	p-value1*	Odds ratio (95% CI)2	Adjusted Odds Ratio3 (95% CI)	p-value2	χ^2 4	R ² N	p-value4
Age									
≥60 Year	0.43	-	0.04	-	-	-			
<60 years	(0.19- 0.97)								
Gender									
Female	0.6	-	0.17	-	-	-			
Male	(0.24-1.26)								
Smoking History									
No Smoking	1.77	-	0.13	-	-	-			
Smoking	(0.84-3.69)								
Duration of warfarin use									
≥1 Year	1.79	-	0.2	-	-	-			
< 1 Year	(0.73-4.37)								
Major drug interactions									
No	0.73	-	0.47	-	-	-			
Yes	(0.3-1.74)								
Herb Use**							2.78	0.854	0.095
Yes	460	291.66	<0.001	72.79	25.33	<0.001			
No	(54.6-3871)	(47.48-1791.84)		(5.69-931.03)	(3.6-185.42)				
Hypofibrinogenemia**									
Yes	179	144.69	<0.001	40.31	19.10	<0.001			
No	(42.6-756)	(36.87-567.88)		(4.86-334.46)	(3.19-114.29)				
INR									
INR ≥3	8.33	7.44	<0.001	4.78	3.69	0.321			
INR <3	(2.16-32.1)	(1.99-27.74)		(0.22-104.86)	(0.33-41.30)				
Weekly Dose									
≥23 mg	1.21	-	0.66	-	-	-			
<23 mg	(0.52-2.83)								
Notes:	* p-value = <0,025			R ² N	= N Nagelkerge	1	= chi-square	3	= Firth Logistic Regression
	**Fisher's Exact test			χ^2	= Chi-square	2	= Binary Logistic	4	= Generalised linear Mode (Herb Use x Hypofibrinogenemia)

therefore excluded from the final model. Although the interaction term approached but did not reach statistical significance ($p = 0.095$), its exclusion is consistent with the clinical interpretation of an additive rather than synergistic combined effect. In the final model, herb use ($aOR = 25.33$, 95% CI: 3.60–185.42; $p < 0.001$) and hypofibrinogenemia ($aOR = 19.10$, 95% CI: 3.19–114.29; $p < 0.001$) remained independently associated with bleeding. The model showed strong explanatory power (Nagelkerke $R^2 = 0.854$), though this may partly reflect the quasi-complete separation in the data (37 of 38

herb users experienced bleeding) rather than genuine model strength. Firth's correction reduced coefficient inflation while preserving explanatory capacity; both associations remained statistically significant, although the wide confidence intervals indicate that precision, rather than robustness, more accurately characterises these estimates

LIMITATIONS

This study has several limitations. The relatively small sample size ($n = 132$) and limited number of bleeding events ($n = 44$) resulted in wide confidence intervals and may have reduced the precision of the estimates. The retrospective design and reliance on electronic medical records introduce the potential for information bias, and patient-reported herb use may introduce recall bias. The single-center setting limits the generalizability of the findings. The role of INR as both a marker of anticoagulation intensity and a potential bleeding risk factor may introduce a degree of circularity that warrants cautious interpretation. Herb use was analyzed as a composite binary variable due to the limited sample size for each herb subtype, which may obscure heterogeneity in bleeding risk across individual



herbal products. Future prospective multicenter studies with larger sample sizes are warranted.

CONCLUSION

Herb use and hypofibrinogenemia each independently associated with bleeding risk in cardiovascular patients on warfarin therapy; the interaction between them was not statistically significant ($p = 0.095$), so these results do not support a synergistic effect. INR remains an important anticoagulation marker, but bleeding risk also depends on haemostatic mechanisms it does not capture. Clinicians should track fibrinogen status and screen for concomitant herbal medicine use to sharpen bleeding risk stratification and manage warfarin therapy mode safely.

CONFLICT OF INTEREST

The author contributed to ideas and thoughts in writing this scientific journal, and declares that there were no conflicts of interest in this study.

DECLARATION OF RELATED PUBLICATION

This manuscript is derived, in part, from data collected for the author's master's thesis entitled

'Analisis Faktor Risiko Penyebab Perdarahan Pasien Rawat Inap Penyakit Kardiovaskular yang Diterapi Warfarin di RSUD Kabupaten Tangerang' (Universitas Pancasila, 2026). The same retrospective case-control dataset ($n = 132$) was also used in a companion manuscript on herbal use and hypofibrinogenemia on clinical implications of bleeding (length of stay, rehospitalization, ICU transfer, and mortality) through descriptive and bivariate analysis, submitted separately for publication. The two manuscripts address different research questions and report non-overlapping primary analyses: the present manuscript focuses on independent bleeding risk factors identified through multivariable Firth's penalized logistic regression,

whereas the companion manuscript is limited to bivariate associations and clinical implications description and does not report adjusted regression results. The authors declare that this does not constitute duplicate or redundant publication.

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REFERENCES

- [1] Stark BA, DeCleene NK, Desai EC, et al. Global, Regional, and National Burden of Cardiovascular Diseases and Risk Factors in 204 Countries and Territories, 1990-2023. *JACC* 2025;86:2167–243. <https://doi.org/10.1016/j.jacc.2025.08.015>.
- [2] Badan Kebijakan Pembangunan Kesehatan, - Indonesian Health Survey 2023 in Numbers. 2024. Project Report. URL: <http://repository.badankebijakan.kemkes.go.id/eprint/5538> n.d.
- [3] Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease. *J Am Coll Cardiol* 2021;77:e25–197. <https://doi.org/10.1016/j.jacc.2020.11.018>.
- [4] Doehner W, Boriani G, Potpara T, et al. Atrial Fibrillation Burden in Clinical Practice, Research, and Technology Development: a Clinical Consensus Statement of The European Society of Cardiology Council on Stroke And The European Heart Rhythm Association. *Europace* 2025;27:euaf019. <https://doi.org/10.1093/europace/euaf019>.
- [5] Hu Y-N, Zhou B-T, Yang H-R, et al. Effect Of Rifampicin on Anticoagulation of Warfarin: a Case Report. *World J Clin Cases* 2021;9:1087–95. <https://doi.org/10.12998/wjcc.v9.i5.1087>.
- [6] Adiyasa MR, Meiyanti M. Pemanfaatan Obat Tradisional di Indonesia: Distribusi dan Faktor Demografis yang Berpengaruh. *J Biomedika Dan Kesehat* 2021;4:130–8. <https://doi.org/10.18051/JBiomedKes.2021.v4.130-138>.
- [7] Zevitra, Mei Nanda, et al. Tingkat Pengetahuan Masyarakat Terhadap Penggunaan Obat Herbal sebagai Pengganti Pengobatan Konvensional di Kelurahan Nusukan, Kecamatan Banjarsari, Surakarta. 2025. *Journal Scientific of Mandalika (jsm)*. DOI: 10.36312/10.36312/vol6iss7pp1850-1861 n.d.
- [8] Harfiani E, Puspita R, Prabarini IRS. Herbal Medicine Usage During the COVID-19 Pandemic in Indonesia: Trends and Determinants. *Sci World J* 2025;2025:1639500. <https://doi.org/10.1155/tswj/1639500>.
- [9] Cross B, Turner RM, Zhang JE, et al. Being Precise with Anticoagulation to Reduce Adverse Drug Reactions: Are We There Yet? *Pharmacogenomics J* 2024;24:7. <https://doi.org/10.1038/s41397-024-00329-y>.
- [10] Tan CSS, Lee SWH. Warfarin And Food, Herbal or Dietary Supplement Interactions: a Systematic Review. *Br J Clin Pharmacol* 2021;87:352–74. <https://doi.org/10.1111/bcp.14404>.
- [11] Mohsenian S, Palla R, Menegatti M, et al. Congenital Fibrinogen Disorders: a Retrospective Clinical and Genetic Analysis of The Prospective Rare Bleeding Disorders Database. *Blood Adv* 2024;8:1392–404. <https://doi.org/10.1182/bloodadvances.2023012186>.
- [12] Wolberg AS. Fibrinogen and Fibrin: Synthesis, Structure, and Function in Health And Disease. *J Thromb Haemost* 2023;21:3005–15. <https://doi.org/10.1016/j.jth.2023.08.014>.
- [13] Ząbczyk M, Ariëns RAS, Undas A. Fibrin Clot Properties in Cardiovascular Disease: From Basic Mechanisms to Clinical Practice. *Cardiovasc Res* 2023;119:94–111. <https://doi.org/10.1093/cvr/cvad017>.
- [14] Putriana NA, Rusdiana T, Rostinawati T, et al. Evaluation of Adverse Drug Reaction in Patients Warfarin Therapy. *J Adv Pharm Technol Res* 2022;13:291–5. https://doi.org/10.4103/japtr.japtr_439_22.
- [15] Fahmi AM, Elewa H, El Jilany I. Warfarin Dosing Strategies Evolution and Its Progress in The Era Of Precision Medicine, a Narrative Review. *Int J Clin Pharm* 2022;44:599–607. <https://doi.org/10.1007/s11096-022-01386-8>.
- [16] Kim S-M, Sohn CH, Kwon H, et al. Thromboelastography as an Early Prediction Method for Hypofibrinogenemia in Emergency Department Patients with Primary Postpartum Hemorrhage. *Scand J Trauma Resusc Emerg Med* 2024;32:85. <https://doi.org/10.1186/s13049-024-01263-5>.
- [17] Dung Chu S, Thi Tran M. Effect of Some Risk Factors on Over-Anticoagulation Disorders and Bleeding in Patients Receiving Anticoagulant Therapy with Overdosage of Vitamin K Antagonist. *Vasc Health Risk Manag* 2023;Volume 19:663–72. <https://doi.org/10.2147/VHRM.S410497>.
- [18] Schlesselman JJ. Sample Size Requirements in Cohort and Case-Control Studies of Disease. *Am J Epidemiol* 1974;99:381–4. <https://doi.org/10.1093/oxfordjournals.aje.a121625>.
- [19] Yqbal M, Laksmiawati DR, Rpp MIJ, et al. Herbal Use and Hypofibrinogenemia on Clinical Implications of Bleeding in Warfarin-Treated Cardiovascular Patients. 2026:15 <https://doi.org/https://doi.org/10.37090/6kw25k55>.
- [20] Zanni S, Del Prete J, Capogrossi A, et al. Influence of Cigarette Smoking on Drugs' Metabolism and Effects: a Systematic Review. *Eur J Clin Pharmacol* 2025;81:667–95. <https://doi.org/10.1007/s00228-025-03817-7>.

- [21] Sombat B, Tongkaew S, Nilwananon A, et al. Incidence and Risk Factors of Warfarin Therapy Complications in Community Hospitals, Central and Eastern Regions, Thailand: A Retrospective, Multicenter, Cohort Study. *BMC Res Notes* 2023;16:104. <https://doi.org/10.1186/s13104-023-06383-2>.
- [22] Hall EH, Sølvsnes MH, Sandberg S, et al. Patient Self-Management of Warfarin Therapy – a Long-Term Follow Up Study. *Thromb J* 2025;23:14. <https://doi.org/10.1186/s12959-025-00694-z>.
- [23] Esen Ş, Özdemir E, Kiriş T, et al. Comparison of Clinical Characteristics, Risk Factors, and Risk Scores of Patients with and without Bleeding Episodes During Warfarin Treatment. *Int J Cardiovasc Acad* 2024. <https://doi.org/10.4274/ijca.2024.00710>.
- [24] Saldanha GDA, Bairros AVD, Paula FR. Theoretical Perspectives on The Interaction Between Warfarin and Garlic Compounds With an *n Silico* Study of CYP3A4. *Saúde St Maria* 2019;3. <https://doi.org/10.5902/2236583436133>.
- [25] Zhuang W, Liu S, Zhao X, et al. Interaction Between Chinese Medicine and Warfarin: Clinical and Research Update. *Front Pharmacol* 2021;12:751107. <https://doi.org/10.3389/fphar.2021.751107>.
- [26] Burkina V, Zamaratskaia G, Rasmussen MK. Curcumin and Quercetin Modify Warfarin-Induced Regulation of Porcine CYP1A2 and CYP3A Expression and activity in vitro. *Xenobiotica* 2022;52:435–41. <https://doi.org/10.1080/00498254.2022.2089932>.
- [27] Khan S-D, Iqbal MS. Predictors of Health-related Quality of Life among Warfarin Patients. *J Pharm Res Int* 2021:439–44. <https://doi.org/10.9734/jpri/2021/v33i62B35715>.
- [28] Iqbal MS, Khan S-D. Sociodemographic Correlates of Warfarin Knowledge in Warfarin Patients. *J Pharm Res Int* 2021:445–50. <https://doi.org/10.9734/jpri/2021/v33i62B35750>.
- [29] Shalansky S, Lynd L, Richardson K, et al. Risk of Warfarin-Related Bleeding Events and Supratherapeutic International Normalized Ratios Associated with Complementary and Alternative Medicine: A Longitudinal Analysis. *Pharmacother J Hum Pharmacol Drug Ther* 2007;27:1237–47. <https://doi.org/10.1592/phco.27.9.1237>.
- [30] Gasse C, Hollowell J, Meier CR, et al. Drug Interactions and Risk of Acute Bleeding Leading to Hospitalisation or Death in Patients with Chronic Atrial Fibrillation Treated with Warfarin. *Thromb Haemost* 2005;94:537–43. <https://doi.org/10.1160/TH05-03-0166>.
- [31] Mai NTQ, Hieu NV, Ngan TT, et al. Impact of Ginkgo Biloba Drug Interactions on Bleeding Risk and Coagulation Profiles: a Comprehensive Analysis. *PLOS ONE* 2025;20:e0321804. <https://doi.org/10.1371/journal.pone.0321804>.
- [32] Li J, Shen N, Luo M, et al. Genetic Characterization of Congenital Fibrinogen Disorders: a Retrospective Analysis of 102 Unrelated Patients in China. *Semin Thromb Hemost* 2025;a-2731-2301. <https://doi.org/10.1055/a-2731-2301>.
- [33] Sillen M, Declerck PJ. Thrombin Activatable Fibrinolysis Inhibitor (TAFI): an Updated Narrative Review. *Int J Mol Sci* 2021;22:3670. <https://doi.org/10.3390/ijms22073670>.
- [34] Hoppensteadt D, Walborn A, Abro S, et al. International Normalized Ratio Relevance to the Observed Coagulation Abnormalities in Warfarin Treated and Those with Disseminated Intravascular Coagulation. *Blood* 2016;128:3797–3797. <https://doi.org/10.1182/blood.V128.22.3797.3797>.



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