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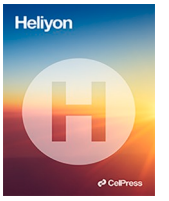

Anticoagulation decision-making before non-cardiac surgery in patients with mechanical heart valve: A retrospective study

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ABSTRACT

Objective: To clarify the timing of warfarin discontinuation at different ranges of INR. Improve anticoagulation management in non-cardiac surgical patients with MHV.
Design: This is a single-center retrospective observational study.
Setting: and participants This study used data from the Hospital Information System, and the Surgery and Anesthesia Information System of the Second Affiliated Hospital of Army Military Medical University. Participants included 121 adult patients with MHV who underwent non-cardiac surgery from 2012 to 2021.
Results: Overall, 121 patients with MHV (15 aortic valve only, 56 mitral valve only, and 50 with multiple valves) underwent non-cardiac surgery. When the duration of warfarin discontinuation was $\leq$ 3 days, 3–5 days, and$\geq$5 days, the INR was 1.45, 1.15, and 1.09, respectively. Bleeding between INR $\leq$1.2 and INR >1.2 groups was not statistically significant using Student's t-test (95% CI −0.57, 0.14 P = 0.24). Multivariate regression analysis revealed that Intraoperative bleeding volume correlated with preoperative albumin levels (OR = 0.68 , 95% CI 0.49, 0.89).
Conclusions: When need preoperative INR is less than 1.5 in patients with MHV undergoing non-cardiac surgery, preoperative warfarin discontinuation for 3 days is sufficient. If INR less than 1.2, preoperative warfarin discontinuation for 3–5 days is appropriate. And in patients with MHV underwent abdominal surgery, intraoperative bleeding is not significant reduced by lower INR after preoperative warfarin discontinuation. Furthermore, the effect of albumin levels on coagulation function cannot be ignored in patients with MHV.
Strengths and limitations: This study was derived from real-world clinical data. It's a retrospectively study to describe the INR changed according to the duration of warfarin discontinuation in patients with MHV and compared intraoperation of bleeding volume between INR>1.2 and INR $\leq$ 1.2after warfarin discontinuation. To clarify the timing of warfarin discontinuation at different ranges of INR. Improve anticoagulation management in non-cardiac surgical patients with MHV, while providing clinicians with a reference for preoperative warfarin adjustment. This study does have a few limitations. The number of cases is small because patients undergoing repeat

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noncardiac surgery after heart valve surgery are a special case population. And the patients were not followed up after non-cardiac surgery. The impact of changes in INR on postoperative complications could not be assessed in patients with MHV.

1. Introduction

Anticoagulants are prescribed for lifelong use after mechanical heart valve (MHV) replacement to prevent thrombosis and possible thromboembolic complications such as valvular thrombosis or major stroke. Anticoagulants include warfarin and non-vitamin K antagonist (VKA) oral anticoagulants such as rivaroxaban and dabigatran. A study has shown that non-VKA oral anticoagulants have some advantages in terms of risk-benefit profile and practicability issues [1]. However, warfarin is considered to be safer than non-VKA anticoagulants and more effective in patients at a high risk of developing atrial fibrillation with valvular heart disease or those with a MHV [2,3]. Presently, warfarin remains the first choice for these patients. Warfarin is a VKA that exerts an anticoagulant effect by interfering with the synthesis of vitamin K-dependent coagulation factors II (thrombin), VII, IX, and X; it has a narrow therapeutic range and many interfering factors. Bleeding is a common complication of warfarin use, and the interaction between warfarin and specific foods, spices, and dietary supplements increases the risk of bleeding [4]. Moreover, age, sex, body weight, liver and kidney function, genetic factors, and patient's compliance with taking warfarin can affect the outcomes; therefore, the anticoagulant effect of the same dose of warfarin differs among different ethnic groups [5,6]. To address the anticoagulation differences of the same dose of warfarin in different populations, the World Health Organization proposed the international normalized ratio (INR) as a standard for modifying the prothrombin time monitoring index to evaluate the anticoagulant effect of warfarin since 1983 [7]. This index helps optimize and monitor warfarin use in clinical settings [8]. Adjusting warfarin dosage by monitoring INR values reduces the risk of bleeding while facilitating the development of disease-specific anticoagulation criteria.

Anticoagulation standards are continuously updated with practice and advances in research. Cannegieter et al. observed that the incidence of bleeding events and thrombotic complications increased significantly in patients with an INR >5.0 or INR <2.0 [9]. According to the 2001 American College of Chest Physicians (ACCP) guidelines, the target range of INR for patients with MHV replacement is 2.0–3.0 [10]. The 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines proposed an optimal INR of 3.0 after mitral valve replacement, whereas the European Society of Cardiology (ESC) guidelines proposed an INR of 3.5 for anticoagulation after MHV replacement [11]. Recently, Zhang et al. concluded that the target range of INR for MHV replacement in Chinese patients is 1.5–2.5 [12]. Although the range of INR values is gradually narrowing and the anticoagulation target values are becoming more defined, there are still differences due to different disease types and countries, and the target range of INR is constantly revised.

Therefore, different countries have different suggestions regarding the timing of warfarin discontinuation before non-cardiac surgery. The American guidelines for regional anesthesia and pain medicine recommended discontinuing warfarin use at least 5 days before planned surgery and the INR to <1.2 prior to initiation of neuraxial block. But European guidelines recommend an INR <1.4 [13]. Though Benzon et al. assessed relevant coagulation factors and reported that an INR <1.2 or warfarin discontinuation for >5 days was necessary to ensure sufficient active coagulation factors to stop bleeding [14], the study population did not include patients with MHV. The incidence rates of stroke, systemic thromboembolism, and cardiovascular death were higher in patients with MHV or atrial fibrillation with valvular disease than in those with non-valvular diseases [15]. Therefore, anticoagulation decision-making is extremely important for perioperative bleeding and thrombus risk assessment when patients with MHV undergo subsequent non-cardiac surgery. Clinically, clinicians pay more attention to coagulopathy caused by warfarin to minimize intraoperative bleeding. However, whether a longer duration of warfarin discontinuation is better remains unclear.

Accordingly, we aimed to assess the relationship between warfarin discontinuation and INR changes.

2. Material and method

2.1. Study design

This is a retrospective observational study. The protocol was approved by the Medical Ethics Committee of the Second Affiliated Hospital of the Army Medical University (ethical approval number: 2021-research 138-01). Due to the retrospective nature of the study, the requirement for informed consent was waived.

2.2. Participants

The participants were 312 patients with MHV underwent non-cardiac surgery at the Second Affiliated Hospital of Army Military Medical University from February 2012 to April 2021. To minimize selection bias, explicit inclusion and exclusion criteria were adopted. The inclusion criteria were age $\geq$18 years, oral warfarin use for >3 months, and non-cardiac surgery. Patients with biological valve replacement, disturbance of consciousness, and/or unavailable relevant case data were excluded.

2.3. Data collection

The data from the Hospital Information System and the Surgery and Anesthesia Information System. Data collected included age, sex, body mass index, type and location of mechanical prosthetic heart valve, type of surgery, medications, laboratory tests, warfarin dose, duration of surgery, bleeding, and complications. Patients were excluded for completely random missing data on laboratory results.

2.4. Variable definitions

The volume of blood loss refers to the total volume of blood lost intraoperatively, which was obtained from the surgical and anesthetic records. Complications include bleeding (intraoperative bleeding >20 g/L), thrombus, postoperative myocardial ischemia. Thrombus, including arterial and venous thromboses, is a clinical stroke confirmed by computed tomography or magnetic resonance imaging. Myocardial ischemia and mechanical valvular disorders were confirmed by electrocardiogram and ultrasonography. Pulmonary embolism and venous embolism of the lower extremities were diagnosed by pulmonary artery computer tomography angiography and ultrasound.

2.5. Statistical analyses

Quantitative data were described in form of mean ± standard deviation and were analyzed using *t*-test. The classification variables were statistically expressed as rate or percentages, and the chi-square test or Fisher's exact probability method was used for statistical tests and comparisons. A multivariate regression analysis was used to identify the influencing factors. A *P*-value <0.05 was considered statistically significant. All statistical analyses were calculated with R version 4.0.4 (The R Foundation, Vienna, Austria).

2.6. Patient and public involvement

No patient involved.

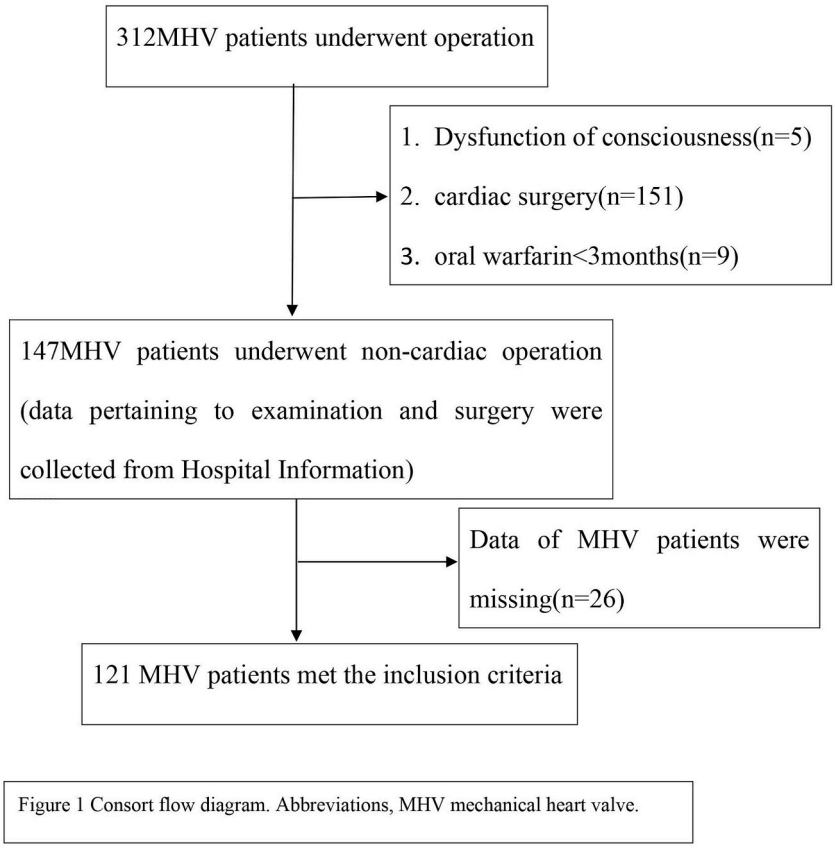

Fig. 1. Flowchart of patient screening.
Abbreviation: MHV, mechanical heart valve.

3. Results

121 patients were included in the statistical analysis. The CONSORT flow diagram is presented in Fig. 1. Baseline demographics are presented in Table 1. The mean age of the patients was 48 years, and the type of valve replacement mainly include mitral replacement (43.6%) and multiple valve replacement (41.3%). Female patients comprised 79.3% of the study population, which was significantly higher than the percentage of male patients.

Patients with different ranges of preoperative INR had differences in atrial fibrillation, BMI, LVEF, warfarin discontinuation and type of anesthesia (Table 2). However, there were no difference in other factors.

The INR changed according to the duration of warfarin discontinuation. When the duration of warfarin discontinuation was $\leq$ 3 days, 3−5 days, and$\geq$5 days, the INR was 1.45, 1.15, and 1.09, respectively (Fig. 2). Warfarin was stopped for >3 days, and the INR was <1.2 in patients with MHV.

The surgeries of 121 patients main included laparoscopic hysterectomy accounted for 38%, laparoscopic cholecystectomy accounted for 31.4%, cesarean section accounted for 11.6%, and the rest of the surgeries accounted for 19% (Table 3).

To identify the relationship between the INR (international normalized ratio of preoperative) and the volume of intraoperative blood loss, patients were divided into two groups. INR$\leq$1.2 and INR >1.2 (95%CI −0.57, 0.14 P = 0.24). In this study, no statistical difference in intraoperative bleeding was observed between the two groups after the patients discontinued warfarin preoperatively (Fig. 3).

To further explore factors associated with intraoperative bleeding, multivariate regression analysis was used (Fig. 4). The volume of operative bleeding was related to preoperative albumin levels (OR, 0.68; 95% CI, 0.49, 0.89).

4. Discussion

In this retrospective study, we observed a wide variation in the duration of preoperative warfarin discontinuation in patients with MHV. The longest discontinuation was 3 weeks and the shortest was 1 day. The data show that most of the INR values greater than 5 days are less than 1.1. Poli et al. observed that the risk of bleeding increased with an INR >3.0 after valve replacement, but they did not study the risk of intraoperative bleeding. When the INR was <2.0, the risk of thrombosis increased significantly [16]. Balancing the risk of bleeding and thrombotic complications is the goal of perioperative attention for patients with MHV who undergo non-cardiac surgery. Clinicians should assess the patient based on their physiological condition, degree of anticoagulation, and risk of bleeding from surgery.

According to the AHA/ACC guidelines, when INR <2.0, the risk of bleeding is lower in oral care, ophthalmology, and dermatology. Warfarin anticoagulation can be continued preoperatively, and few gastrointestinal endoscopic procedures can also be performed; however, other major operations and invasive procedures should be comprehensively evaluated by doctors according to the patient's

Table 1
Baseline characteristics of patients with MHVs (n = 121).

Characteristics	Values
Age (years)	48.6 ± 11.2
Female patients	96 (79.3)
BMI	24.8 ± 3.3
Duration of warfarin use (years)	6.2 ± 5.3
Warfarin dose (mg)	3.20 ± 1.14
Duration of warfarin discontinuation	
Short ($\leq$3 days)	53 (43.8%)
Medium (>3 and$\leq$5days)	35 (28.9%)
Long (>5days)	32 (26.4%)
Atrial fibrillation	37 (30.6)
INR before warfarin discontinuation	2.1 ± 0.6 m
INR after warfarin discontinuation	1.3 ± 0.3
Type of MHVs	
Aortic valve	15 (12.4)
Mitral valve	56 (46.3)
Multiple valves	50 (41.3)
Chronic disease	
Hypertension	11 (9.1)
Diabetes	5 (4.1)
Stroke	3 (2.5)
Other	4 (3.3)
Complication	13 (10.7)
Hemorrhage	2 (1.7)
Valve obstruction	1 (0.8)
Myocardial ischemia	10 (8.3)

Values are presented as mean ± standard.
deviation or n (%). Abbreviations: BMI, body mass index. INR, international normalized ratio. MHV, mechanical heart valve.

Table 2
Comparison of different range INR of preoperative.

	INR ≤ 1.2	INR>1.2	P
n	65	55	
Age	48.39 ± 11.42	48.88 ± 11.06	0.822
Gender			0.665
Female	50 (76.9)	54 (81.8)	
Male	15 (23.1)	10 (18.2)	
Duration of warfarin use (years)	6.08 ± 4.49	6.32 ± 6.02	0.802
BMI	25.31 ± 3.42	24.07 ± 3.42	0.042
Atrial fibrillation	15 (23.1)	23 (41.8)	0.045
Warfarin discontinuation (days)	4.23 ± 3.12	5.92 ± 3.17	0.023
Duration of surgery (minutes)	107.46 ± 77.25	101.42 ± 76.42	0.250
Bleeding (mL)	186.00 ± 292.87	131.09 ± 211.94	0.471
Complication	6 (9.2)	27 (12.7)	0.749
Warfarin dose (mg)	3.14 ± 1.09	3.29 ± 1.21	0.462
ALT	36.8 ± 63.46	19.96 ± 13.01	0.055
ALB	42.37 ± 4.35	43.48 ± 4.71	0.182
Creatinine	63.81 ± 21.31	63.52 ± 19.57	0.938
HGB	119.88 ± 20.93	114.93 ± 23.34	0.223
PLT	189.54 ± 74.19	164.62 ± 72.05	0.714
LVEF	65.08 ± 4.36	62.93 ± 6.46	0.032
VitaminK_1 (preoperative antagonism)	2 (3.1)	7 (12.7)	0.099
Prosthetic type			0.875
Aortic valve	7 (10.9)	8 (14.0)	
Mitral valve	30 (46.9)	26 (45.6)	
Double valves	27 (42.2)	23 (40.4)	
Anesthesia type			0.024
General anesthesia	51 (78.5)	52 (94.5)	
Spinal anesthesia	14 (21.5)	3 (5.5)	

Abbreviations: INR, international normalized ratio of preoperative. BMI, body mass index. ALT, alanine transaminase. ALB, albumin. HGB, hemoglobin. PLT, platelet. LVEF, left ventricular ejection fraction.

condition [17]. Surgery can be divided into three categories according to risk of surgical bleeding: minimal, low or moderate, and high bleeding risk procedures [18]. The warfarin dose does not need to be adjusted for minimal-risk surgeries, including cataract surgery, tooth extraction, and implantable cardioverter-defibrillator implantation; however, warfarin should be discontinued before low- and high-risk surgeries [19]. This study included high bleeding risk surgeries, including major orthopedic surgeries, urologic or gastrointestinal surgeries, spinal surgeries, and moderate bleeding risk procedures, including laparoscopic cholecystectomy and abdominal/laparoscopic hysterectomy. All patients with MHV in this study were required to discontinue warfarin use preoperatively. However, there is no consensus on the duration of warfarin discontinuation. European guidelines recommended an INR <1.5 for high-risk surgery. The AHA guidelines recommend short-term interruption (≤5 days) for patients with a low risk of thrombosis in aortic valve replacement [17,20]. White et al. interrupted warfarin use and monitored the INR changes in patients (excluding those with MHV) treated with warfarin (deep venous thrombosis, atrial fibrillation without valvular disease, and prophylactic warfarin anticoagulation), and they suggested that if the INR is between 2 and 3 or <1.2, warfarin should be discontinued for approximately 4–5 days, and if the INR is > 3.0, the duration of warfarin discontinuation would be longer [21]. The results of this study showed that patients with MHV who discontinued warfarin for ≥3 days had an INR <1.2. However, when the duration of warfarin discontinuation greater than 5 days, longer withdrawal time does not result in greater benefit. Zhang et al. observed that the incidence of severe complications was approximately 11.3% when the INR was <1.0 [12]. In the study, One patient with an INR of 0.82 died because of MHV dysfunction, and a patient with an INR of 0.92 had postoperative gastrointestinal bleeding. Moreover, there was no statistical difference in intraoperative bleeding volume between the groups with INR >1.2 and INR ≤1.2 after warfarin discontinuation. As a result, the duration of warfarin discontinuation is too long to better in patients with MHV. Low INR values also can lead to thromboembolism, which can seriously endanger the life of patients with MHV. The INR returned to normalized (≤1.2) after 3–5 days of warfarin discontinuation. If warfarin is discontinued for more than 5 days, the risk of thromboembolism could be increases as the INR decreases.

The patients of our study stopped using warfarin and instead used bridging with low-molecular-weight heparin preoperatively, the incidence of bleeding was 1.7%, no bleeding-related death occurred. The incidence of thromboembolism was 0.8%, but one died. Although the incidence of bleeding increases after bridging therapy, most bleeding cases can be reversed and treated, and no fatal risk exists. Once thromboembolism occurs, mortality or disability increases. Bridging is used to shorten the no-anticoagulation period in clinical practice. Although there is no evidence that surgery increases the risk of arterial thrombosis, surgical stress can lead to thrombocytopenia, increased adhesions, and a potential risk of thrombosis. The guidelines of the AHA/ACC, ESC, and ACCP suggested that warfarin-induced anticoagulation can be continued for low-risk surgeries; however, warfarin should be discontinued, and low-molecular-weight heparin should be used for bridging before moderate- and high-risk bleeding procedures [22–24].

There is growing evidence that low serum albumin levels are associated with several cardiovascular diseases, including ischemic heart disease, heart failure, atrial fibrillation, stroke, and venous thromboembolism [25]. Paar et al. reported that low albumin levels

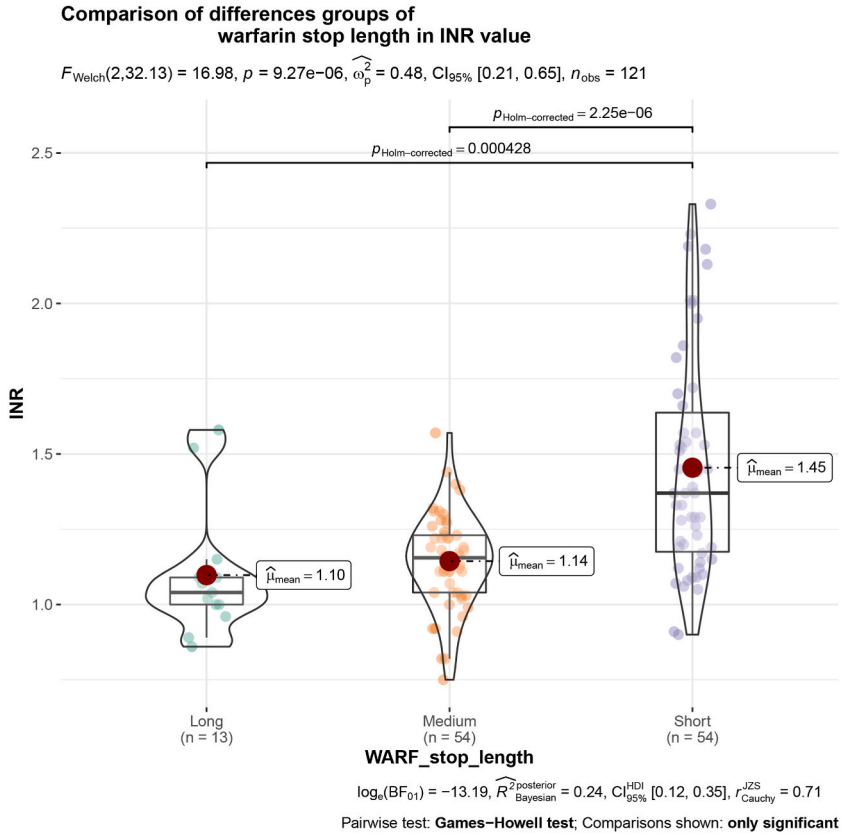

Fig. 2. INR value in different duration of Warfarin discontinuation.
Abbreviations: INR, international normalized ratio.
The duration of warfarin discontinuation is ≤ 3 days, 3–5 days, and >5 days.

Table 3
Type of surgery and proportion of MHV patients.

Type of surgery	n (%)
Caesarean Section	14 (11.6)
Laparoscopic cholecystectomy	38 (31.4)
Laparoscopic Transvaginal hysterectomy	46 (38.0)
Tension-free repair for groin hernia	3 (2.5)
Laparoscopic pancreatoduodenectomy	1 (0.8)
Laparoscopic radical prostatectomy	1 (0.8)
Transurethral resection of bladder tumor	2 (1.7)
Laparoscopically assisted resection of gastrointestinal tumors	4 (3.3)
Heap lobectomy	1 (0.8)
Chest incision debridement surgery and skin flap transplantation	3 (2.5)
Posterior lumbar interbody fusion	2 (1.7)
Hip replacement surgery	2 (1.7)
Middle cerebral artery thrombectomy	1 (0.8)
Radical thyroidectomy	1 (0.8)
High ligation of great saphenous vein	1 (0.8)
Maxillary cystectomy	1 (0.8)
Total	121 (100)

might contribute to the occurrence of venous thromboembolism [26]. This might be related to the physiological properties of serum albumin, including anti-inflammatory, antioxidant, anticoagulant, antiplatelet aggregation activities, and colloid osmotic effects. We demonstrated that albumin levels negatively correlated with the volume of intraoperative bleeding, which further proved the anti-coagulant effect of albumin; it was clear that the level of albumin would also influence the blood coagulation state of patients. Therefore, the patient's albumin level should be considered when adjusting for anticoagulation during the perioperative period.

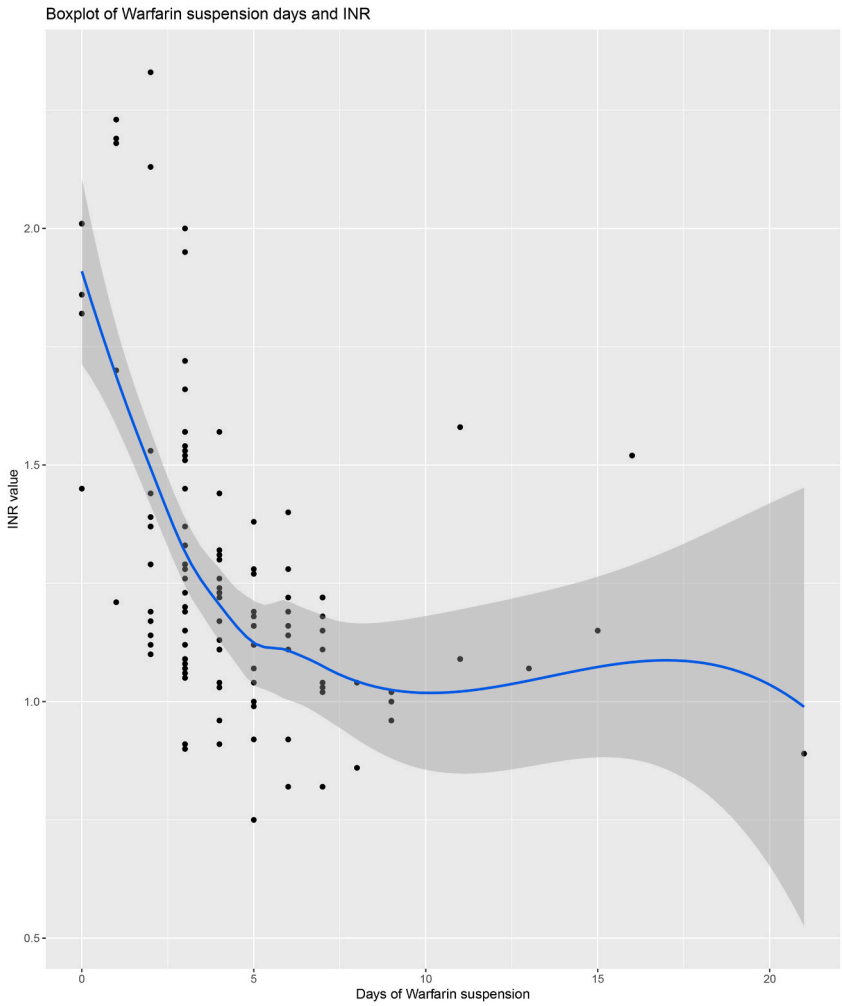

Fig. 3. *Comparison of bleeding volume between INR > 1.2 and INR < =1.2 after warfarin discontinuation.*
Abbreviation: INR, international normalized ratio.

5. Limitations

This is a single-center retrospective study and may be subject to selection bias. Meanwhile, Retrospective studies infer causes from existing results, and the intensity of causal arguments is weak. Factors influencing intraoperative bleeding during noncardiac surgery in patients with MHV need to be confirmed by further prospective trials.

6. Conclusions

When need preoperative INR is less than 1.5 in patients with MHV undergoing non-cardiac surgery, preoperative warfarin discontinuation for 3 days is sufficient. If INR less than 1.2, preoperative warfarin discontinuation for 3–5 days is appropriate. And in patients with MHV underwent abdominal surgery, intraoperative bleeding is not significant reduced by lower INR after preoperative warfarin discontinuation. Furthermore, the effect of albumin levels on coagulation function cannot be ignored in patients with MHV.

Author contribution statement

Yan Liang contributed to conceive the experiments, perform the experiments, analyze and interpret the data, and write the paper. Guiying Yang contributed to perform the experiment. Hong Li contributed data. Ning Ding contributed to materials. Lin Zhang contributed to analysis tools and analyzed the data. Jian chen contributed to design the experiments and contribute reagents.

		bleeding CLASS	
Predictors	*Odds Ratios*	*CI*	*p*
Gender [Male]	0.73	0.06 – 6.47	0.782
Age	1.00	0.91 – 1.10	0.993
BMI	0.82	0.59 – 1.10	0.207
Anesthesia type [spinal anesthesia]	0.71	0.03 – 18.80	0.833
Duration of surgery	1.01	1.00 – 1.02	**0.027**
Warfarin dose	1.34	0.66 – 2.91	0.421
Warfarin discontinuation	1.16	0.88 – 1.52	0.262
ALB	0.68	0.49 – 0.89	**0.011**
HGB	1.03	0.97 – 1.10	0.408
PLT	0.99	0.97 – 1.00	0.180
Chronic disease [Yes]	0.94	0.10 – 6.19	0.948
Observations	120		
R^2 Tjur	0.346		

Fig. 4. Multivariate analysis of intraoperative bleeding.
Abbreviations, BMI body mass index. ALB albumin. HGB hemoglobin. PLT platelet.

Patient and public involvement

Patients and/or the public were not involved in this research.

Data sharing statement

No additional data are available.

Author contribution statement

Yan Liang: Conceived and designed the experiments; Perform the experiments; Analyze and interpret the data; Wrote the paper.
Guiying Yang: Perform the experiment.
Hong Li, Ning Ding and Lin Zhang: Contributed reagents, materials, analysis tools or data.
Jian Chen: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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