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Research on Effects of Comorbidities Disease on Anticoagulation and Bleeding Disorders Risk in Patients with Overdosage of Vitamin K Antagonist Anticoagulant

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Abstract

Objectives: Research on effects of comorbidities disease on anticoagulation overdose in patients receiving anticoagulant therapy with vitamin K antagonists anticoagulant (VKAs) drugs at HaiPhong-VinhBao International General Hospital. **Methods:** Description and Prospective study. Research on 79 patients receiving anticoagulant therapy with VKAs who have an INR testing index of more than anticoagulation dose with VKAs and check INR every 4 weeks. **Results:** The average research age is 65.65 ± 12.17 years [33: 85], most of the elderly group. The Male group is lower than the female group ($p > 0.05$). Patients with hemorrhage signs account for 22.8%. The INR testing index has an average value is 5.88 ± 3.0 [3.02 - 23.95]; The group of INR > 5 level is a higher risk of bleeding than the group of INR ≤ 5 levels, there is statistical difference ($p < 0.001$). Patients using anti-vitamin K drugs on the background of patients with many complicated conditions are easily at risk of bleeding, especially in patients with renal falure and musculoskeletal disease are the cause of the increased risk of bleeding with the rate of the difference is OR = 3.64 (CI: 1.17 - 11.32, with $p < 0.05$) and OR = 3.52 (CI: 1.19 - 10.47, with $p < 0.05$) of statistical significance. **Conclusion:** All most patients with anticoagulation overdose are in the elderly group. The group with INR > 5 levels has a higher risk of bleeding than the group with INR ≤ 5 levels, it's the statistical significance ($p < 0.001$). The comorbidities Diseases such as hypertension, ischemic heart disease, coronary stents, old myocardial infarction, Graves, and gastritis all have the risk of increasing the risk of bleeding when taking anticoagulants but not yet statistically significant (have OR > 1 but $p > 0.05$); Patients used VKAs drugs on the background of kidney failure or arth-

ritis pathology are the cause of the increased risk of bleeding, it's statistical significance ($p < 0.05$).

Keywords

Comorbidities Disease, INR, VKAs, Bleeding Disorders

1. Introduction

Coagulation disorders in patients taking vitamin K antagonist anticoagulants (VKAs) when treating patients with cardiovascular disease that cause blood clots. VKAs are coumarin derivatives, including warfarin, acenocoumarol, phenprocoumon, and ethylbiscoumacetate when treating patients with atrial fibrillation, valve artificial heart, severe left atrial dilatation, etc. complications can occur [1] [2] [3]. Vitamin K plays an important role in coagulation because vitamin K is a fat-soluble vitamin necessary for the synthesis of coagulation factors involved in the coagulation cascade and plays an important role in the regulation of blood clotting, which is necessary for the assistance of blood clotting [2] [4]; When complications occur, it is a medical emergency accounting for about 11% of cases [5] or more [2] [3] [4]. Many cases of late arrival or late detection can lead to severe blood loss, hemodynamic instability, hemorrhagic shock, and even hemorrhagic stroke [6] [7] requiring both resuscitation and intervention and/or emergency surgery [3] [5] [8] [9].

In recent years, Hai Phong-Vinh Bao International General Hospital, Vietnam has been put into operation and has quickly provided medical examination and treatment to serve people in the community from many domestic and international regions. In the past time, there have been many cases of medical examination and treatment with coagulation disorders requiring timely emergency treatment, of which the majority of patients are taking anticoagulants with vitamin K antagonists and stem from many causes. Factors or factors that lead to blood clotting disorders. Vitamin K anticoagulants are drugs used to treat cardiovascular diseases that cause embolism to prevent thromboembolic complications caused by atrial fibrillation. valve disease is, an artificial heart valve, prevention of thromboembolic complications, and pulmonary embolism in hip surgery [9] [10] [11]; however, along with such benefits, the use of anticoagulants also often has side effects, including coagulation disorders, the most common manifestation of which is bleeding complications, bleeding may occur, occurs throughout the body such as the central nervous system, extremities, visceral organs, intra-abdominal, intraocular, subcutaneous, etc. Sometimes diarrhea and joint pain occur individually. In some cases, signs of vasculitis, liver damage, hair loss, localized skin necrosis, and allergic skin rashes [2] [12] [13]. Vietnam has also had a number of studies on this topic, However, in order to study in depth the factors affecting blood clotting disorders, there are still quite a few

studies and there are still many great unknowns related to the process of blood clotting disorders that are still open in the world [2] [12] [13] [14]. Therefore, we conducted this study with the main objective of "Study on effects of comorbidities disease on anticoagulation and bleeding disorders risk in patients with overdosage of vitamin K antagonist anticoagulant".

2. Research Methods

2.1. Participants

Research on 79 cases of patients with blood clotting disorders when they come to outpatient medical examination and treatment at Hai Phong-Vinh Bao International General Hospital, Vietnam during the period from 2/2021 to 11/2022.

Patients receiving anticoagulant therapy with vitamin K antagonists who have an INR above the required threshold are assessed by the INR test, with the usual target range of 2.5 - 3.5 for pregnant patients mechanical prosthetic heart valves, and 2 - 3 in the remaining cases. Patients adhere to the dose and time of INR testing periodically every 4 weeks. An overdose of anticoagulants (INR > 3.5 for patients with prosthetic heart valves and INR > 3.0 in the rest) can cause bleeding or doses that are too low to work can cause bleeding. blocks [3] [5] [10].

2.2. Research Design

Research Design: Cross-sectional descriptive study.

Sample Size Formula: Applying the formula for calculating sample size for cross-sectional descriptive research [4] [5].

$$n = \frac{z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

where: n is the sample size; p (prevalence) is the population proportion (select p = 11%) [5]; d is the margin of error (confidence interval): 0.1 [4] [5]; α (Level of error): 0.05; Z-value is 1.96. We calculate the sample size according to the above formula to get the result is n = 37, to increase the accuracy, we duplicated the sample size above to get a sample size of n = 74.

Research Data Processing: All collected data were processed on a computer using IBM SPSS 23.0 software. Use odds ratio analysis OR (OR: Odds ratio—compares the odds of the outcome between one exposure group and a second exposure group) with a 95% confidence interval (95% CI). Statistical significance level < 0.05 was used to evaluate the significant relationship in the analyzed statistics.

- If OR > 1, the risk factor increases the likelihood of having the disease compared with the possibility of not having the disease.
- If OR = 1, there is no association between the risk factor and the likelihood of disease.
- If OR < 1, then risk factors can reduce the likelihood of having the disease compared with the possibility of not having the disease [3] [5].

3. Results

3.1. Basic Characteristics and Clinical Characteristics of the Study Group

The results of the basic characteristics of this research (Table 1) showed that the average age of the study group was 65.65 ± 12.17, the oldest patient was 85 years old and the youngest was 33 years old; the young group accounted for 26.6% and the elderly group accounted for 73.4% with $p > 0.05$. The male group's 25 patients (31.65%) and the Female group's 54 patients (68.35%) with $p > 0.05$. The average value of INR was 5.88 ± 3.0 [3.02 - 23.95]. The group with an INR level > 5 has a high risk of bleeding 41/79 patients (51.9%), while the group with an INR level ≤ 5 has a low risk of bleeding 48.1%, showing that the proportion of patients with coagulation disorders was detected. with INR levels at the high-risk and low-risk thresholds were similar ($p > 0.05$). Patient with hemorrhage signs has 18 patients (22.9%), Group with INR > 5 has 17/18 patients (94.44%) while Group with INR < 5 has 1/18 patients (5.56%) with $p = 0.0001$ (<0.001).

Table 1. Basic characteristics of the study group.

Characteristics	Average value (Percentage), n = 79	
Gender	Male: 29	29/79 (36.7%)
	Female: 50	50/79 (63.3%)
Age (years):	65.65 ± 12.62 [33 - 85]	
Age group: Young group and elderly group	Young group (≤60 years): 21	21 (26.6%)
	Elderly group (>60 years): 58	58 (73.4%)
Divided into 3 age groups (years):	Young group (<40 years old): 2	2/79 (2.5%)
	Middle-age group (40 - 60 years old): 19	19/79 (24.1%)
	Elderly group (>60 years old): 58	58/79 (73.4%)
Body Mass Index (BMI)	23.19 ± 3.51 [17 - 28]	
Degree of obesity	Obesity: 30	30/79 (38%)
	Non-obesity: 49	49/79 (62%)
Heart rate (cycle/min)	83.11 ± 19.91 [50: 158]	3.02 - 23.95
Systolic blood pressure	120.76 ± 15.48 [80: 180]	
Diatolic blood pressure	71.56 ± 10.57 [48: 100]	
INR Value	5.88 ± 3.0	3.02 - 23.95
Degree of INR	INR ≤ 5: 38	38/79 (48.1%)
	INR > 5.0: 41	41/79 (51.9%)
	$p > 0.05$	
Bleeding complications	n = 18	18/79 (22.9%)
Degree of INR group	INR group > 5: 17	17/18 (94.44%)
	INR group ≤ 5: 1	1/18 (5.56%)
	$p < 0.001$	

Clinical Characteristics: Among the 178 patients who showed symptoms, the most common symptom was shortness of breath found in 14/79 (17.7%), chest palpitations were found in 10/79 (12.7%), chest pain was found in 8/79 (10.1%), Swollen joint pain was 11/79 (13.9%), Fast heart rate was 5/79 (6.3%), Fatigue/weakness was 6/79 (7.9%), Nausea/Vomiting was 4/79 (5.1%), Shock/Dizziness was 3/79 (3.8%). The proportion of patients with bleeding symptoms was 18/79, accounting for 22.8%, of which severe bleeding complications accounted for 6/79 cases (7.6%). Symptoms of bleeding with the main sign of bleeding under the skin accounted for 11/79 (13.9%), bleeding gums accounted for 4/79 (5.1%) and there was one case with nosebleeds due to bleeding; It is quite rare that signs of gastrointestinal bleeding account for 2/79 (2.5%) and subconjunctival hemorrhage occurs in one case accounting for 1.3%. We observed that the main diseases in the study, there are 31 patients with Atrial fibrillation (45.6%), 35 patients with Heart valve disease who had surgery (44.3%), and 8 patients with Heart valve disease without surgery but with atrial fibrillation or heart failure accounted for 10.1%.

The results in Table 2 showed that the Comorbidities disease in these patients with heart failure or heart failure with improved function were the most common, accounting for 58.2%, atrial fibrillation and fluttering for 55.7%, hypertension (50.6%), then diabetes (10.1%), Renal failure (24.1%), valvular heart disease who had heart valve disease has surgery and heart valve disease without surgery (heart valve disease but not yet operated) accounted for 30.4% and 41.8%, respectively, group of patients with cerebral infarction accounted for 17.7%,

Table 2. Risk factors of the comorbidities disease.

No	Comorbidities disease	Quantity (Percentile)
1	Hypertension	40 (50.6%)
2	Diabetes	8 (10.1%)
3	Heart failure	46 (58.2%)
4	Renal failure	19 (24.1%)
5	Atrial fibrillation	44 (55.7%)
6	Heart valve disease has surgery	24 (30.4%)
7	Heart valve disease without surgery	33 (41.8%)
8	Cerebral infarction	14 (17.7%)
9	Ischemic heart disease	40 (50.6%)
10	Coronary artery stents	11 (13.9%)
11	Old myocardial infarction	3 (3.8%)
12	Basedow	7 (8.9%)
13	Hypothyroidism	5 (6.3%)
14	Musculoskeletal disease	26 (32.9%)
15	Gastritis	18 (22.8%)

ischemic heart disease is also common (50.6%), coronary artery stents accounted for 13.9%, myocardial infarction accounted for 3.8%, Basedow and hypothyroidism less common 8.9% and 6.3%, gastritis accompanied by 22.8%, the rate of patients admitted to the hospital with Musculoskeletal disease (Musculoskeletal with swelling and pain in the joints) accounted for 32.9%.

3.2. Factors of the Comorbidities Disease Related to Anticoagulation Disorder and Bleeding Risk in Patients Taking Vitamin K Antagonist Anticoagulant

Table 3 showed that diseases such as hypertension, ischemic heart disease, coronary stents, old myocardial infarction, Graves, and gastritis all have the risk of increasing the risk of bleeding when taking anticoagulants but are not yet statistically significant ($p > 0.05$). In addition, comorbidities such as renal failure (24.1%) and musculoskeletal disease (32.9%) are very clear risk factors that increase the risk of bleeding with OR, respectively OR = 3.64 and OR = 3.52 (both have OR > 1), with $p < 0.05$.

4. Discussion

4.1. Basic Characteristics and Clinical Characteristics of the Study Group

The results (Table 1) showed that the majority of patients in the study group

Table 3. Multivariate analysis of comorbidities disease factors associated with bleeding risk.

No	The comorbidities disease	Odds ratio OR	95% CI	P
1	Hypertension	4.07	0.91 - 18.32	0.074
2	Diabetes	0.45	0.12 - 1.78	0.215
3	Heart failure	0.87	0.30 - 2.51	0.501
4	Renal failure	3.64	1.17 - 11.32	0.027
5	Atrial fibrillation	0.99	0.35 - 2.87	0.599
6	Heart valve disease has surgery	0.85	0.27 - 2.73	0.516
7	Heart valve disease without surgery	0.86	0.29 - 2.51	0.499
8	Cerebral infarction	0.51	0.10 - 2.53	0.327
9	Ischemic heart disease	1.29	0.45 - 3.72	0.418
10	Coronary artery stents	3.53	0.93 - 13.36	0.067
11	Old myocardial infarction	7.5	0.64 - 88.05	0.128
12	Basedow	1.4	0.25 - 7.91	0.505
13	Hypothyroidism	0.84	0.09 - 8.01	0.681
14	Musculoskeletal with Painful swelling of joints	3.52	1.19 - 10.47	0.022
15	Gastritis	2.89	0.92 - 9.14	0.066

belong to the elderly group, which is quite consistent with the research of other authors as the majority of patients fall into the elderly group, although the average age in many studies has an average age. The average is higher in our study because most of these countries have a higher life expectancy than Vietnam [8] [13] [14]. The study had a rather high percentage of females compared with the male group but there was no statistically significant difference ($p > 0.05$). Some studies show that males are taller than females but the difference is not statistically significant; Gualtiero P (1996) shows a roughly equal ratio of men to females (43% of women while males have a higher proportion of 57%) [3], Connolly S shows a higher proportion of male than female but There was no significant difference [8].

The statistical results (**Table 1**) show that the proportion of patients with coagulation disorders detected with INR levels at the high risk of bleeding (INR level > 5) and low-risk thresholds (INR level ≤ 5) were similar ($p > 0.05$). Most of the patients accounting for 17/18 (94.44%) with signs of bleeding were in the group with INR > 5, while there was also 1 case of bleeding with INR = 4.82 in the INR group ≤ 5 ($p < 0.001$) with subcutaneous hemorrhage at the tips of the toes seen in patients with atrial fibrillation-heart failure is taking anticoagulants with Vitamin K antagonists and has timely treatment by us when patients come for medical examination and treatment at the hospital; therefore, it is necessary to manage and manage patients well when detecting INR > 5, but for patients with coagulopathy whose index is not too high in the INR ≤ 5 group, it is still necessary to monitor and evaluate their clinical status. ready for timely treatment when there are signs of bleeding [9] [10].

The pathophysiological causes of the increased risk of bleeding events are multifactorial [2]; They may be a direct consequence of urea-associated platelet dysfunction or impaired platelet adhesion and aggregation; impaired platelet glycoprotein IIb or IIIa receptor activation and subsequent glycoprotein binding [5] [10]. Vitamin K is a group of fat-soluble vitamins that are structurally similar and play an important role in the regulation of blood clotting, which is necessary for the assistance of blood clotting [3] [5] [9].

The proportion of patients with bleeding symptoms was 22.8%, of which severe bleeding complications accounted for 7.6%. Symptoms of bleeding with the main sign of bleeding under the skin bleeding accounted for 13.9%, bleeding gums accounted for 5.1% and there was one case with nosebleeds due to bleeding. Thrombocytopenia; it is quite rare that signs of gastrointestinal bleeding account for 2.5% and subconjunctival hemorrhage occurs in one case accounting for 1.3%.

Our study encountered a higher bleeding rate than some other studies such as the study of Eichinger S. in 2016 in Austria with a bleeding rate of about 11% [5]; the result of our study is that this rate is higher because the hospital is due to the role of a regional general hospital where development in the field of cardiology and emergency medicine with more specialized specialties than many

neighboring hospitals, so it is easier for patients to choose to come for check-up and follow-up when they have an abnormal sign; Furthermore, some patients do not really compliance with the patient's medication dose, many patients had the habit of using functional foods that interact with VKAs drugs, or many patients still habit of using a lot of green vegetable foods with rich in vitamin k because the surrounding areas had a tradition of growing green vegetables… Besides, the research on the use of warfarin has increased, and bleeding from warfarin use is a prevalent reaction and an important cause of mortality as a review article published (2001, USA) reported that the incidence of major bleeding in patients prescribed warfarin ranged from 0% to 16%, and the incidence of fatal bleeding was 0% to 2.9%. These data are consistent with literature reports of major bleeding frequencies for warfarin as high as 10% to 16% (Wysowski DK *et al.*, 2007) [4].

However, Karen EG (2004) also showed that the rate of bleeding can be up to 10% but in fact, up to 25% of patients are likely to bleed at least once per year [9]. Our study has not encountered any case of cerebral hemorrhage, however, the presence of bleeding under the eye conjunctiva also suggests a high risk of cerebral hemorrhage due to the structure of the cerebral arteries and the structure of blood vessels in the eye have similarities; Connoly S.J. (2009) showed a serious complication rate with a hemorrhagic stroke rate of 3.36% and a mortality rate of 4.13% per year in the warfarin group [8].

The main disease to indicate the use of vitamin K antagonist anticoagulants is mainly atrial fibrillation, with atrial flutter accounting for 45.6%, and a valvular disease with heart valve surgery also accounts for 44.3%, the rest is the group of valvular heart valve disease without heart valve surgery but with atrial fibrillation or heart failure accounted for 10.1% (**Table 2**) as the same some other studies [3] [9]; However our study has a higher rate of patients with atrial fibrillation and valvular disease than some other studies such as Karn EG *et al.* found 35% of patients with atrial fibrillation and 20% of patients with valvular disease had surgery [11]. The results (**Table 2**) showed that the Comorbidities disease in these patients with heart failure or heart failure with improved function, atrial fibrillation, and fluttering, hypertension, ischemic heart disease were the most common, and Renal failure (24.1%), rate of patients admitted to the hospital with swelling and pain in the joints (32.9%) and other some comorbidities [14].

4.2. Factors of the Comorbidities Disease Related to Anticoagulation Disorder and Bleeding Risk in Patients Taking Vitamin K Antagonist Anticoagulant

The results of the study evaluating the association between comorbidities disease and the risk of bleeding complications in patients taking anticoagulants with VKAs in **Table 3** show that diseases such as hypertension, ischemic heart disease, coronary artery stents, old myocardial infarction, Graves, and gastritis all have the risk of increasing the risk of bleeding when taking anticoagulants but not yet statistically significant ($p > 0.05$), possibly because larger sample size is

needed to confirm this issue; Unless comorbidities such as renal failure (24.1%) and musculoskeletal disease (32.9%) are very clear risk factors that increase the risk of bleeding with OR = 3.64 and OR = 3.52, respectively (both have OR > 1), with statistically significant ($p < 0.05$).

Vitamin K is a fat-soluble vitamin necessary for the synthesis of many factors of the coagulation cascade. Factors II, VII, IX, and X are all important for the intrinsic and common pathways of coagulation. Vitamin K also synthesizes Protein C, Protein S, and Protein Z, anticoagulation proteins that degrade specific coagulation factors, preventing excessive thrombosis following the initial coagulation cascade. Therefore, in the case of patients who have a Vitamin K deficiency is associated with impaired coagulation function and excessive bleeding and hemorrhage; this can be caused by poor diet, malabsorption in the intestines, or liver failure. This enzyme is called tenase, and converts prothrombin to thrombin, beside that Calcium and phospholipids are required cofactors for prothrombin activation enzyme complexes to function [1] [2] [5].

Evaluation of patients with comorbidities disease on kidney failure may find that in patients with comorbidities kidney failure disease that can affect multiple organs in the body, a severe decrease in kidney function can lead to a buildup of toxins and impurities in the blood, patients with renal failure may have two simultaneous risks for vascular problems: increased susceptibility to blood clots; Because kidney failure does not eliminate all toxins, these substances will stick to the walls of the blood vessels, causing blood vessels to become blocked, thereby causing the risk of blood clots leading to an increased risk of thrombosis. Stroke, in addition to renal failure also leads to a paradox because the impaired renal function will cause vascular dysfunction that can lead to a tendency to form hemorrhagic microvessels that increase the risk of hemorrhagic events; Furthermore, patients with end-stage renal disease (ESRD) will be subjected to frequent invasive diagnostic and therapeutic strategies, such as central vascular access and hemodialysis (plus regular heparin thereafter), which may also increase the risk of bleeding [3] [9] [11] [12]. Evidence from a multicenter study by Shah M. (2014) (Quebec and Ontato, Canada) showed that warfarin use in dialysis patients versus no warfarin was associated with an increased risk of hemorrhagic stroke. significantly higher (odds ratio OR 1.44; 95% confidence interval, 1.13 - 1.85) [7]. Chan *et al.* studied a cohort of 1671 patients with atrial fibrillation who were on hemodialysis and found that the risk, including stroke and death, was 1.9 times higher with warfarin use [7]. In another study, Wizemann *et al.* reported that the use of warfarin in a group of patients with atrial fibrillation older than 75 years (n = 107) undergoing hemodialysis was associated with a 2-fold increased risk of stroke and death, 2 times [7]. Winkelmayer *et al.* also conducted a retrospective cohort study in hemodialysis patients with atrial fibrillation that found warfarin use was associated with a 2.4-fold increased risk of hemorrhagic stroke [7]. In fact, the use of anticoagulants in patients with renal failure are usually VKAs and direct oral anticoagulants (DOACs) [2] [10]. It

should therefore be noted that in these patients there are both beneficial and adverse effects of taking vitamin K anticoagulants. The use of anticoagulants in patients with renal failure is usually VKAs and DOACs [2] [10]. It should therefore be noted that in these patients there are both beneficial and adverse effects of taking vitamin K anticoagulants. The use of anticoagulants in patients with renal failure is usually VKAs and DOACs [2] [10]. It should therefore be noted that in these patients there are both beneficial and adverse effects of taking vitamin K anticoagulants.

Some studies showed that Vitamin K is cartilage proteins and dependent bone, while VKAs such as acenocoumarol and warfarin affect the functioning of other vitamin k dependent proteins such as matrix Gla protein (MGP) that is an essential inhibitor of vitamin for cartilage calcification, MGP is also a genetic variant in a vitamin K dependent protein and associated with VKAs, acenocoumarol or warfarin act as anticoagulants through inhibition of vitamin K dependent blood coagulation proteins, so the use of VKAs significantly increases the risk of progression of osteoarthritis pathogenesis by inhibiting the vitamin k pathway, therefore it represent a modifiable risk factor [15] [16]. In patients with musculoskeletal diseases, quite a lot of people who are being treated with anticoagulants come to the doctor with swelling and pain in the joints (the proportion of patients who come to the doctor with swelling and pain in the joints accounts for 32.9%), among these, it is worth checking with coagulation disorders and common manifestations if there are bleeding complications, most of which are bruises under the skin, which are easily confused with musculoskeletal pathology, simple joint or adrenal insufficiency pathology; In addition, the bleeding tendency may be the result of people with musculoskeletal diseases often using anti-inflammatory pain relievers such as non-steroidal anti-inflammatory drugs, etc., which may increase the risk of bleeding when combined with anticoagulants [12] [13] [16].

Therefore, the elderly are a complex group of patients and are likely to have many comorbidities. Attention to comorbidities is critical to ensure that all factors are taken into account when planning a treatment strategy with vitamin K antagonists [9]; finally, the need for close clinical monitoring as well as the need to adjust the dose during the treatment of each patient in order to control the INR within safe limits for treatment and prevention of thrombosis is extremely important, patients need to be regularly checked and monitored for blood clotting function during monitoring and treatment.

5. Conclusions

The average age of the study subjects was mostly in the elderly group. The average value of INR was 5.88 ± 3.0 [3.02 - 23.95], the proportion of patients with bleeding symptoms accounted for 22.8% and severe bleeding complications accounted for 7.6%. The group with a high-risk INR (INR > 5) caused coagulopathy and a higher risk of bleeding than the group with a low-risk INR (INR ≤ 5)

with $p < 0.001$.

It is recommended that VKAs be used with caution in patients with complex underlying medical conditions. The comorbidities diseases such as hypertension, ischemic heart disease, coronary stents, old myocardial infarction, graves, and gastritis all have the risk of increasing the risk of bleeding when taking anticoagulants but not yet statistically significant (have $OR > 1$ but $p > 0.05$); Especially in patients with renal failure (24.1%) and musculoskeletal disease (32.9%) when overdosed with anticoagulation was at risk of bleeding with odds ratio $OR = 3.64$ (CI: 1.17 - 11.32) with $p < 0.05$ and $OR = 3.52$ (CI: 1.19 - 10.47) with $p < 0.05$, respectively, the difference is statistically significant ($p < 0.05$).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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