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► To cite this version:

Farès Moustafa, Loïc Dopeux, Aurelien Mulliez, Yves Boirie, Christine Morand, et al.. Severe undernutrition increases bleeding risk on vitamin-K antagonists. *Clinical Nutrition*, 2021, 40 (4), pp.2237-2243. 10.1016/j.clnu.2020.10.002 . hal-03031024

HAL Id: hal-03031024

<https://hal.science/hal-03031024>

Submitted on 30 Nov 2020

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Severe undernutrition increases bleeding risk on vitamin-K antagonists

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Word count abstract: 250

Word count article (excluding title page, abstract, references, tables): 2850

Keywords: Undernutrition; Bleeding; Anticoagulant agent; Micronutrient.

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Abstract

Introduction. Hemorrhage occurs in 7 to 10% of patients treated with vitamin K antagonist (VKA), with major bleeding in 1 to 3%. Impact of nutritional status on the bleeding risk of patients on anticoagulants is still poorly documented. Our study aimed to analyze the link between the nutritional status of patients on VKA and the occurrence of hemorrhagic events. We also analyzed micronutrients status.

Methods. A case-control, monocentric, and prospective study was conducted from August 2012 to October 2015. The case patients were those presenting with major bleeding and control patients those without any bleeding under VKA treatment.

Results. Overall, 294 patients under VKA treatment were paired according to age, gender, and index normalized ratio (INR). Out of these, 98 (33.3%) had major bleeding and 196 (66.7%) did not have any bleeding. Additionally, more than two-thirds of patients displayed undernutrition, which was more prevalent in bleeding than non-bleeding patients (OR = 1.85, CI95%: 1.07 - 3.21). There was a higher bleeding risk for those with severe undernutrition (OR = 2.66, CI95%: 1.58 - 4.46), with no difference found concerning moderate undernutrition. Bleeding patients had lower plasma-zinc concentrations than non-bleeding patients (9.4 ± 3.6 vs. $10.5 \pm 3.7 \mu\text{mol/L}$, $p = 0.003$); among them, there was a higher rate of patients with plasma zinc under $5 \mu\text{mol/L}$ (9% vs. 2%, $p < 0.001$).

Conclusion. Patients with undernutrition on VKA exhibit a significantly higher bleeding risk, which increases three-fold in case of severe undernutrition. The evaluation of nutritional status provides additional, valuable prognosis information prior to initiating VKA therapy.

ClinicalTrials.gov number: NCT 01742871

Introduction

Vitamin-K antagonists (VKA) are the most common anticoagulants used to prevent cerebrovascular events in patients with atrial fibrillation or a mechanical valve. VKA therapy is also employed to prevent and treat patients with venous thrombosis.[1] A bleeding event is an essential complication of anticoagulant therapy. Every year, hemorrhage events occur in 7–10% of patients treated with VKA, including major bleeding in 1–3% [2,3] The literature has described many factors that explain the occurrence of hemorrhagic stroke, [4] including index normalized ratio (INR) >4.5 [5], age over 80 years old, female gender, weight, genetic polymorphisms like those encoding cytochromes P4502C9 or VKORC1 [6], catabolic or comorbid conditions, such as congestive heart failure, liver and renal failure, and diabetes [7], as well as polymedication, which can generate drug interactions.[4,8–10]

Many studies have examined the influence of vitamin K in food and the risk of INR imbalance in patients on VKA.[11] These studies assert that a regular and moderate intake of vitamin K allows for a better index normalized ratio (INR) balance under antivitamin K.[12] However, only a few studies have investigated patients' nutritional status and its impact on the bleeding risk of patients on anticoagulants. Some authors have shown that protein-energy undernutrition is a risk factor for INR imbalance,[8] while others have reported that specific micronutrients likely interfere with the maintenance of coagulation homeostasis. For example, vitamin-C deficiency increases the risk of bleeding;[13] Copper (Cu) deficiency exposes the patient to inhibition of thrombogenesis and platelet aggregation, and prolongs prothrombin and bleeding times;[14,15] acute depletion of zinc stores alters platelets and their aggregation, thereby resulting in prolonged bleeding times.[16–18]

Therefore, the present study assessed the link between the nutritional status, specifically the undernutrition, of patients under VKA treatment and the occurrence of hemorrhagic events. We also analyzed the role of micronutrients in the occurrence of hemorrhages.

Material and methods

Inclusion criteria

Patients were included in the study that were over 18 years old, on VKA, with INR over 1.5, and that had been admitted to the emergency unit of the Clermont-Ferrand university hospital, France. We excluded pregnant women, patients with pacemakers or implantable defibrillators, and patients with mechanical cardiac valves.

All patients were included after obtaining their signatures for informed consent.

This research was approved by the appropriate French research ethics committee (CPP Sud-Est VI, IRB number: 00008526) and declared on clinicaltrials.gov (NCT 01742871).

Study design

A case-control, monocentric, and prospective study was conducted from August 2012 to October 2015. The case patients were those presenting with major bleeding under VKA treatment, in accordance with the French definition,[19] and the control patients were those without any bleeding on VKA treatment. Control and case patients were paired according to age, gender, and INR, with a ratio of one case for every two control patients. In this study, bleeding was considered major if the clinician in charge of the patient used reversal therapy with prothrombin complex concentrate (PCC).

The primary endpoint was the diagnosis of protein-energy undernutrition, which is defined as undernutrition (either weight loss $\geq 10\%$ within six months, weight loss $\geq 5\%$ within one month, body mass index (BMI) $\leq 21\text{Kg/m}^2$, albumin $< 35\text{g/L}$, prealbumin between 50–110mg/L, or MNA score < 17), or severe undernutrition (either weight loss $\geq 15\%$ within 6 months, weight loss $\geq 10\%$ within one month, BMI $\leq 18\text{Kg/m}^2$, albumin $< 30\text{g/L}$, or prealbumin $< 50\text{mg/L}$).[20] We also calculated the fat and fat-free mass compartment using bioelectrical impedance analysis for all included patients, the value of which was compared to the value for healthy adults.[21–23]

The secondary endpoints were the assessment of different plasma micronutrients, whose values were then compared with normal thresholds (vitamin B1, vitamin C, zinc, and copper [Cu]), along with the nutritional risk index (NRI)[24], Beyth bleeding-risk score[25], and Pronostic Inflammatory and Nutritional Index (PINI) score.

Baseline variables

We collected data pertaining to demographics, indication for anticoagulant therapy, anticoagulant type, length of treatment, previous bleeding events on VKA, related treatments, physical examination, weight at one and six months, height, BMI, and laboratory analyses for INR, prothrombin time (PT), platelet count, albumin/prealbumin, c-reactive protein (CRP), orosomucoid, zinc, Copper (Cu), Selenium, vitamin B1, vitamin C, and creatinine. For zinc blood sample, we analyzed plasma and erythrocyte concentration because if most of blood concentration was erythrocyte zinc, plasma concentration is a good reflect of zinc protein binding which could be impacted by undernutrition.

Statistical analysis

Justification for the number of subjects involved was based on a power simulation with recruitment capacity. It similarly considered data from literature exploring the relationship between undernutrition state and bleeding risk under VKA treatment. In 2011, in our hospital, there were 162 prothrombin complex concentrate (PCC) orders to reverse VKA for a major bleeding accident over 46,000 patients admitted in our emergency unit. Thus, to show a different rate of undernutrition patients between the controls and case group, 300 patients (200 controls per 100 cases) would provide the trial with 90% power to detect a minimum difference of 13%, at two-sided significance level of $\alpha = 0.05$.

Moreover, faced with the difficulty of evaluating the expected difference between the two groups, two analyses were also planned for ethical reasons (the risk of overestimating the number of patients) and methodological reasons (the re-estimation of the expected difference). For 75 patients (50 controls and 25 cases), the difference would be significant at 0.018 [26]. For 150 patients (100 controls and 50 cases), the difference was significant and equal to 0.031 [26].

Statistical analyses were performed using STATA 15.0 (StataCorp, College Station). Qualitative variables were expressed in terms of numbers and associated proportions, while quantitative variables were reported in terms of numbers, mean, and the associated standard deviation, median, and range.

Graphic representations are included with these analyses wherever possible.

Description are always global and by group (patients under antivitamin-K treatment, with or without a severe hemorrhagic event that required care in the emergency department). Comparisons between groups (anthropometric and biological, treatment) were systematically conducted without adjusting (either a chi2 test or Fisher's exact test for qualitative parameters and Student's t-test or Mann–Whitney test for

quantitative variables). A multivariable logistic regression model was performed to analyze severe bleeding. Covariates entered in the model were selected according to their statistical significance ($p < 0.2$ in univariate analysis). [27] Results are shown as odd ratio with their 95% confidence interval). All statistical tests were carried out at the risk of error of the first species $\alpha = 5\%$ (except interim analysis).

For the analysis of the primary endpoint, which is the rate of patients considered undernourished, the comparison between the two groups was performed using a chi² test or Fisher's exact test, when appropriate.

Secondary endpoints, which are the rate of micronutrient-deficient patients and endothelial dysfunction, were analyzed in a similar manner to that described for the qualitative parameters. Concerning comparisons between independent groups of quantitative variables (body composition measured by bio-impedancemetry, PINI, and RNI), data were analyzed using a Student test or Mann–Whitney U test. In case of unsatisfied t-test conditions, normality was verified using Shapiro-Wilk test and homoscedasticity using Fisher–Snedecor test.

Since observational studies do not allow for conclusions to be drawn in terms of causality, the study considered the use of so-called propensity scores, which were first proposed by Rosenbaum and Rubin.[28] This was used as a sensitivity analysis, in order to validate the classical multivariate model. Confounding factors were selected statistically, according to their statistical relationship with both the outcome (severe bleeding) and the main covariate assessed (undernutrition). Propensity score was performed using ordered logistic regression with undernutrition as dependent variable and confounding factors as covariates. Then we performed the same multivariate analysis (or severe bleeding) with logistic regression, with an inverse weighting on this propensity score calculated.

Results

From August 2012 to January 2014, 294 patients under VKA treatment were paired: 98 (33.3%) patients with major bleeding and 196 (66.7%) without bleeding.

The mean age was 81.9 ± 7.8 years old, with most (77.4%) of the patients on VKA for atrial fibrillation. The age and gender ratio were similar between bleeding and non-bleeding patients (**Table 1**). However, history of bleeding events was twice as high for bleeding versus non-bleeding patients (23% vs. 10.5%, $p = 0.004$, respectively), while the bleeding-risk score (Beyth score) was higher for bleeding versus non-bleeding patients (1.8 ± 0.7 vs. 1.5 ± 0.7 , $p = 0.005$, respectively).

Biological analyses revealed that bleeding patients displayed higher platelet counts than non-bleeding patients (276.9 ± 100.7 vs. 236.8 ± 74.7 g/L, $p = 0.001$, respectively). Biochemical and micronutrient characteristics are provided in **Table 2**. With regards to biological-nutritional data, bleeding patients exhibited lower albumin levels than non-bleeding patients (30.9 ± 4.9 vs. 33.4 ± 6.1 g/L, $p < 0.001$, respectively), without any significant difference observed for prealbumin levels. Accordingly to the micronutrient analysis, bleeding patients had lower plasma zinc levels than non-bleeding patients (9.4 ± 3.6 vs. 10.5 ± 3.7 $\mu\text{mol/L}$, $p = 0.003$, respectively), involving a higher rate of patients with plasmatic zinc levels under $5 \mu\text{mol/L}$ (9% vs. 2%, $p < 0.001$, respectively). No differences were detected regarding plasma Cu, vitamin C, or vitamin B1 levels.

Accordingly, to the nutritional status, more than two-thirds of patients had undernutrition. Global undernutrition prevalence was higher in bleeding than non-bleeding patients (OR = 1.85, CI95%: 1.07 - 3.21), with over a two-fold higher bleeding risk for those with severe undernutrition (OR = 2.66, CI95%: 1.58 - 4.46), whereas no

difference was detected considering moderate undernutrition (**Table 3**). Moreover, bleeding patients had a lower NRI score (88.1 ± 8.1 vs. 91.8 ± 9.6 , $p < 0.01$, respectively) and lower fat mass (28.1 ± 9.7 % vs. 30.8 ± 9.8 %, $p = 0.03$, respectively) than non-bleeding patients but without difference for fat free mass.

Interestingly, there were several differences identified with respect to the bleeding sites (**Table 4**). Patients with intracranial bleeding exhibited lower INR values and higher vitamin B1 levels than those with other bleeding sites. Patients with gastrointestinal bleeding displayed lower PINI scores than those with other bleeding sites. Patients with muscular hematoma presented higher CRP levels, higher orosomucoid rates, and higher PINI scores than those with other bleeding sites. However, no difference was found in undernutrition status between different bleeding sites.

Multivariable analysis revealed that patients with severe undernutrition (OR = 2.83, CI95%: 1.34-5.99) or bleeding history (OR = 3.49, 95%IC: 1.63-7.51) or showed an increased bleeding risk (**Table 5**). As shown in **Figure 1**, our multivariable analysis, which included severe undernutrition and history of bleeding, showed the best predictive value for bleeding complications during VKA treatment (AUC 0.70, CI95%: 0.63-0.77), and was significantly better than PINI score (AUC 0.53, CI95%: 0.46-0.61). As no major difference between the main multivariable analysis and the sensitivity analysis with inverse propensity matching were noticed, we do not show these results.

Discussion

The present study demonstrates that there is a significantly higher bleeding risk for patients with an undernutrition status and that are under VKA treatment. In this large cohort of 294 patients on VKA, bleeding patients exhibited a higher global undernutrition status than non-bleeding patients, with nearly a two-fold higher bleeding risk. Moreover, we have demonstrated that severe undernutrition results in a three-fold higher bleeding risk under VKA treatment.

Surprisingly, very few studies have paid attention to the nutritional status' impact on bleeding risk under VKA treatment, despite major bleeding being one of the latter's most feared outcomes. In our study, severe undernutrition was revealed to be a bleeding risk factor that was as high as a history of major bleeding, involving a three-fold higher bleeding risk. Indeed, a history of major bleeding is one of the most essential risk factors that are included in different bleeding-risk scores.[29] One study has shown that protein-energy undernutrition is a risk factor for INR imbalance, in terms of the therapeutic imbalance factors of antivitamin K and the hemorrhagic consequences in geriatric practice.[8] Conversely, cases of low INR or resistance to VKA have been described in subjects receiving a diet that is rich in protein and low in carbohydrates, without increased amounts of foods containing vitamin K.[30]

Identifying poor nutritional status remains a challenge for physicians, despite various methods and indexes for nutritional evaluation being advocated and used to predict unfavorable prognoses in some clinical settings.[31] In our study, bleeding patients on VKA were shown to display lower NRI scores and lower fat mass than non-bleeding patients. The NRI is a simple, well-validated tool for identifying patients at risk for nutrition-related complications and may therefore be a valuable tool for identifying

patients with nutritional depletion, prior to significant body wasting.[32] In stable heart-failure patients, the NRI is strongly associated with appetite-regulating hormones, inflammatory markers, and metabolic markers, while indicating nutritional depletion. Additionally, low NRI is associated with an increased death incidence.[33] A new international consensus for defining undernutrition was very recently obtained, through an crucial collaboration between the American (ASPEN) and European clinical nutrition societies (ESPEN). [34] These new phenotypic and etiological criteria were not considered in this study, given that our study was initiated before this new definition was proposed.

In this study, serum albumin levels were lower in bleeding than non-bleeding patients. Although the serum albumin level is not solely an accurate indicator of nutritional status, it was used in the NRI and PINI scores. However, meta-analysis revealed that hypoalbuminemia (which is defined as a serum albumin concentration of less than 34 g/L) could be used as an outcome predictor in acutely ill patients.[35] Moreover, albumin is the most abundant plasma protein and contributes to the transport of drugs. Warfarin, a specific VKA, is primarily bound to serum albumin, meaning that hypoalbuminemia is likely to increase the free fraction of warfarin, thereby increasing the risk of major bleeding.[36] In patients under 75 years old, hypoalbuminemia was a significant predictor of all bleeding events (minor and major).[37] Hypoalbuminemia is similarly associated with age-related frailty and could thus reflect underlying conditions and diseases that in their turn facilitate bleeding. Thus, albumin could easily be considered a biological parameter for the benefit-risk balance of preventing VKA bleeding events in clinical practice.

With regards to micronutrient assays, we only found a difference between the rates of plasma-zinc levels. In our study, bleeding patients had lower plasmatic zinc levels than non-bleeding patients, with a higher patient proportion with plasmatic zinc under 5 μ mol/L among bleeders. The clinical impact of plasma-zinc deficit aligns with its biological action, as zinc deficit can increase bleeding time [14,15]. Furthermore, *in-vitro* results have demonstrated that zinc and Cu are linked to Cu-ZN superoxide dismutase and can impact intracranial bleeding due to hypertension.[38] Unfortunately, we were unable to detect any statistical difference, between bleeding and non-bleeding patients, for other micronutrients like Cu, vitamin C, or vitamin B1. Unexpectedly, regarding the bleeding site, we found that patient with intracranial bleeding showed a higher level of vitamin B1 which is contradictory with some case reports showing that hemorrhages in the brain, indicating a disruption of the blood-brain barrier, is characterized by a vitamin B1 deficiency. [39–41] However, these cases reports were about rats or patients with Wernicke's encephalopathy. An interesting means of analyzing the impact of micronutrients on bleeding risk would be to analyze patient diets. Unfortunately, we didn't analyze the patient diet in our study. However, some diet like the Mediterranean diet's, with abundance of fruits and vegetables, is well recognized for its containing many antioxidant nutrients.[42] This diet has been reportedly demonstrated to reduce cardiovascular events but with higher bleeding times, which is likely to impact bleeding complications.[43,44]

To our knowledge, this is the first study to focus on the nutritional status of bleeding complications in patients under VKA treatment. Nevertheless, our study has several limitations that must be acknowledged. First, patients were recruited in one single center, which may have generated less reproducibility, despite the avoidance of

practice variability among different centers. However, data were collected prospectively using a case-control design and the number of included patients was remarkable; therefore, our data thus provide a useful basis for future controlled clinical trials. Second, since we focused solely on major bleeding, the mean age of our population was higher (81.9 years old) than that observed in other studies that examined patients on VKA treatment. This could render it difficult to generalize these results.[45] One possible explanation could be that most of our patients (77.4%) were on VKA treatment for atrial fibrillation and that we had chosen bleeders as case subjects. However, patients over 75 years old show a higher bleeding risk and most are at risk of undernutrition; owing to these facts, they represent a likely population of interest for evaluating the bleeding risk. Third, there was no external adjudication of major bleeding events, which align with the French definition of major bleeding.[19] However, prior studies have demonstrated that adjudicated data are usually well matched with onsite outcome assessments.[46,47]

Conclusion

The present study has demonstrated that there is a significantly higher bleeding risk for patients on VKA that display undernutrition, which is three-fold higher in case of severe undernutrition. With regards to micronutrients, we found lower plasma-zinc levels in bleeding patients, along with a higher rate of patients showing levels under 5 μ mol/L. Therefore, we can conclude that the evaluation of nutritional status may provide additional, valuable prognosis information about the benefit-risk balance for older patients, prior to the initiation of VKA therapy.

Acknowledgments

All authors had full access to all study data (including statistical reports and tables) and bear responsibility for data integrity and accuracy. All authors were involved in the critical revision of the manuscript, with regard to its primary intellectual content, and all authors approved the final version that has been submitted for publication.

Statement of Authorship

F Moustafa, L Dopeux and J Schmid designed the study and had final responsibility for study supervision. A Mulliez had the responsibility of data analysis. F Moustafa, Y Boirie, C Morand, E Gentes, D Richard, N Farigon, A Lebreton, D Teissandier and F Dutheil participated to the revising the intellectual content. Each author critically reviewed and participated in revising the manuscript, and each author approved the final version.

Declaration of interest

Dr. Moustafa has served as a consultant for Bayer HealthCare Pharmaceuticals and Sanofi; has been a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi; and has received grants from LFB.

Dr. Schmidt has received payments for board membership from Bayer HealthCare Pharmaceuticals, Daichi, Lilly, and Pfizer, as well as personal compensation from Biomerieux, Bohringer Ingelheim, Sanofi, and Novartis.

All other authors declare that they have no relationships that are relevant to the contents of this paper.

Research Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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Table 1: Clinical Characteristics in case and control patients under VKA

	All patients N= 294		Case N= 98		Control N= 196		<i>p-value</i>
Sex gender							
Men, n (%)	126	(41,9%)	42	(42,0%)	84	(42,0%)	<i>1.000</i>
Women, n (%)	174	(57,8%)	58	(58,0%)	116	(58,0%)	
Age							
Age, mean (SD)	81.9	(7,8)	82.4	(7,9)	81.7	(7,8)	<i>0.481</i>
Medical History							
Renal insufficiency, n (%)	54	(17.9%)	16	(16.0%)	38	(19,0%)	<i>0.524</i>
Cardiac insufficiency, n (%)	254	(84.4%)	82	(82.0%)	172	(86,0%)	<i>0.365</i>
Stroke, n (%)	61	(20.3%)	21	(21.0%)	40	(20,0%)	<i>0.839</i>
Cardiac infarct, n (%)	61	(20.3%)	15	(15.0%)	46	(23,0%)	<i>0.105</i>
History of bleeding, n (%)	44	(14.6%)	23	(23.0%)	21	(10,5%)	<i>0.004</i>
VKA agent							
Fluindione, n (%)	198	(65.8%)	68	(68.0%)	130	(65,0%)	<i>0.605</i>
Warfarin, n (%)	67	(22.3%)	20	(20.0%)	47	(23,5%)	<i>0.493</i>
Acenocoumarol, n (%)	31	(10.3%)	11	(11.0%)	20	(10,0%)	<i>0.789</i>
VKA indication							
Atrial fibrillation, n (%)	233	(77.4%)	75	(75.0%)	158	(79,0%)	<i>0.433</i>
Venous thromboembolism, n (%)	23	(7.6%)	5	(5.0%)	18	(9,0%)	<i>0.220</i>
Pulmonary hypertension, n (%)	1	(0.3%)	1	(1.0%)	0	(0,0%)	<i>0.333</i>
Beyth score , mean (SD)	1.6	(0.7)	1.8	(.7)	1.5	(0,7)	<i>0.005</i>

Abbreviations: SD, standard deviation; VKA, vitamin K antagonist*

Table 2: Biological and micronutrients characteristics in case and control patients under VKA

	All patients N=294		Case N=98		Control N=196		p- value
Prothrombin time in %, Mean (SD)	19,3	(11.4)	19,0	(11.4)	19.5	(11,4)	0,711
INR, Mean (SD)	4,4	(2.3)	4,6	(2.5)	4.3	(2,2)	0,292
1.5 ≤ INR < 2, n (%)	12		3	(12%)	9	(18%)	
2 ≤ INR ≤ 3, n (%)	34		12	(48%)	22	(44%)	
3 < INR ≤ 5, n (%)	13		5	(20%)	8	(16%)	
INR > 5, n (%)	16		5	(20%)	11	(22%)	
Hematocrit in %, mean (SD)	36.7	(7.3)	31.5	(8.1)	39.3	(5,2)	<0.001
Platelet count in Giga/L, mean (SD)	250.2	(86.4)	276.9	(100.7)	236.8	(74,7)	0.001
Creatinine in μmol/L, mean (SD)	95.7	(46.5)	95.6	(45.4)	95.7	(47,2)	0.579
Albumin in g/L, mean (SD)	32.6	(5.8)	30.9	(4.9)	33.4	(6,1)	<0.001
Prealbumin in mg/L, mean (SD)	196.5	(69.8)	189.9	(62.4)	199.7	(73,1)	0.394
CRP in mg/L, mean (SD)	48.0	(62.8)	44.9	(56.0)	49.6	(65,9)	0.542
Orosomucoïd in mg/L mean (SD)	1280.4	(477.5)	1289.6	(464.9)	1276.1	(483,2)	0.826
Erythrocyte Zync in μmol/L, mean (SD)	126.8	(76.1)	131.8	(105.5)	124.1	(53,9)	0.506
Plasma Zync in μmol/L, mean (SD)	10.1	(3.7)	9.4	(3.6)	10.5	(3,7)	0.003
- Under 5 μmol/L, n (%)	13	(4.3%)	9	(9.0%)	4	(2,0%)	
Plasma Cuper (Cu) in mg/L, mean (SD)	18.0	(5.4)	18.3	(5.2)	17.8	(5,5)	0.427
Selenium in μg/l, mean (SD)	68.2	(33.8)	65.5	(21.4)	69.6	(38.9)	0.314
Vitamin C in μmol/L, mean (SD)	22.0	(18.4)	22.6	(19.4)	21.4	(18,1)	0.763
- Under 3 μmol/L, n (%)	39	(13.0%)	14	(14.0%)	25	(12,5%)	
Vitamin B1 in μg/L, mean (SD)	53.6	(19.3)	53.8	(24.2)	53.5	(16,4)	0.924

Abbreviations: SD, standard deviation; INR, index normalized ratio; CRP, C-reactive protein

Table 3: Nutritional characteristics in case and control patients under VKA

	All patients N= 294		Case N= 98		Control N= 196		p-value
Undernutrition, n (%)	200	(68.0%)	75	(76.5%)	125	(63.8%)	<i>0.027</i>
Severe undernutrition, n (%)	90	(30.6%)	44	(44.9%)	46	(23.5%)	<i><0.001</i>
Moderate undernutrition, n (%)	110	(36.9%)	31	(31.6%)	79	(40.3%)	<i>0.185</i>
<i>Nutritional assessment</i>							
Weight (Kg), mean (SD)	73.2	(1.0)	71.8	(1.6)	73.9	(1.3)	<i>0.32</i>
BMI, mean (SD)	27.1	(5.5)	26.4	(5.0)	27.5	(5.7)	<i>0.08</i>
NRI score, mean (SD)	90.6	(9.2)	88.1	(8.1)	91.8	(9.6)	<i><0.01</i>
PINI score, mean (SD)	23.54	(62.7)	17.97	(34.9)	26.15	(72.1)	<i>0.48</i>
Fat-free mass in kg, mean (SD)	50.9	(11.6)	51.2	(10.4)	50.7	(12.3)	<i>0.73</i>
Fat mass in %, mean (SD)	29.8%	(9.8%)	28.1%	(9.7%)	30.8%	(9.8%)	<i>0.03</i>

Abbreviations: SD, standard deviation; NRI, nutritional risk index; PINI, Pronostic Inflammatory and Nutritional Index

Table 4: Clinical characteristics at baseline in patients who suffered major bleeding on VKA therapy “Case patients” according to bleeding site (N=98)

	Intracranial bleeding N=10	Gastrointestinal bleeding N=33	Muscular bleeding N=29	Others N=26	P-value
Gender, n (%)					
Men	3 (30%)	17 (51.5%)	11 (37.9%)	10 (38.5%)	0.571
Women	7 (70%)	16 (48.5%)	18 (62.1%)	16 (61.5%)	
Age, mean (SD)	80.1 (12.1)	83.8 (6.8)	82.4 (7.5)	80.9 (7.9)	0.43
Biological, mean (SD)					
INR	2.71 (0.92)	4.5 (2.5)	5.1 (45)	4.8 (2.8)	0.015
Albumin in g/L	34.2 (5.2)	30.7 (4.4)	29.9 (4.4)	31.3 (5.6)	0.13
Prealbumin in mg/L	184 (63.6)	200.9 (60.5)	195.3 (63.9)	171.25 (62.0)	0.49
Creatinin in µmol/L	73.9 (23.8)	100.0 (59.7)	95.9 (38.9)	98.0 (36.1)	0.26
CRP in mg/L	40.3 (50.9)	17.9 (25.9)	77.9 (61.8)	37.9 (52.0)	<0.001
Platelet count in Giga/L	253.6 (95.7)	294 (90.1)	281.6 (85.2)	261.4 (135.5)	0.28
Orosomuroid in mg/L	1104 (541)	1161 (357)	1538 (509)	1254 (438)	0.02
PINI score, median (IQR)	3.8 (0.3-12.5)	1.31 (0.5-6.6)	13.1 (5.2-55.4)	4.1 (1.4-9.8)	<0.001
NRI score, mean (SD)	94.2 (7.9)	87.4 (7.75)	86.6 (7.5)	88.5 (8.5)	0.9
Micronutrient, mean (SD)					
Plasmatic Cuper in mg/L	17.6 (5.6)	16.9 (4.5)	18.7 (5.2)	20.1 (5.6)	0.109
Vitamin B1 in µg/L	66.2 (16.6)	49.8 (20.9)	57.7 (31.6)	49.6 (21.2)	0.026
Vitamin C in µmol/L	26.45 (24.8)	26.7 (19.7)	15.2 (13.5)	23.2 (23.3)	0.08
Erythrocyte zinc in µmol/L	142.4 (64.7)	125.9 (51.9)	104.5 (38.9)	160.2 (187.9)	0.18
Plasmatic zinc in µmol/L	10.1 (4.9)	10.2 (7.9)	9.64 (3.2)	9.7 (4.2)	0.9
Selenium in µg/l	75.8 (24.6)	67.4 (19.1)	61.5 (20.9)	63.8 (22.9)	0.36
Undernutrition, n (%)	7 (70%)	26 (78.8%)	24 (82.8%)	8 (30.8%)	0.605
Severe undernutrition, n (%)	2 (20%)	16 (48.5%)	14 (48.3%)	12 (46.1%)	0.439

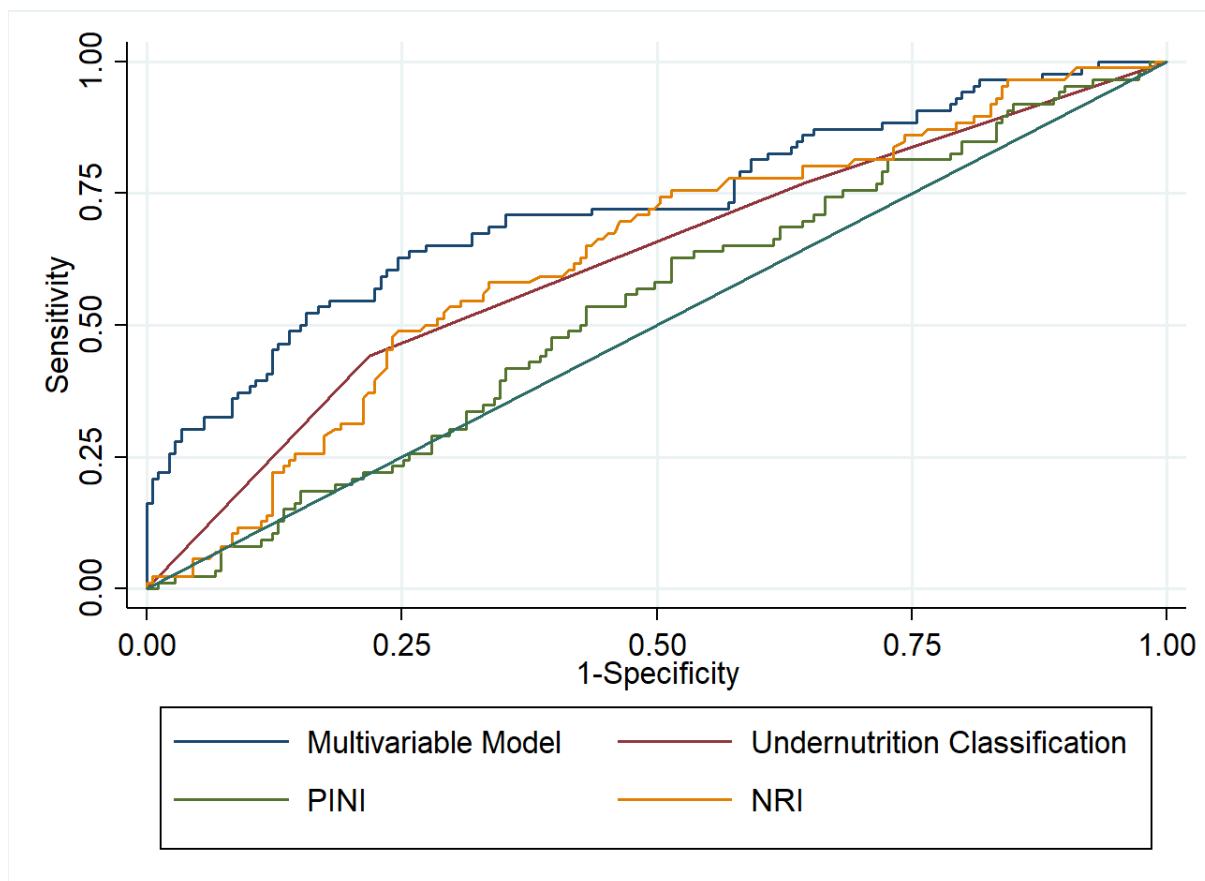
Abbreviations: SD, standard deviation; VKA, vitamin K antagonist; INR, index normalized ratio; CRP, C-reactive protein; IQR, interquartile rang ; NRI, nutritional risk index; PINI, Pronostic Inflammatory and Nutritional Index.

Table 5: Multivariable analysis

	Odds ratio	CI95%	p-value
No undernutrition	ref		
Non severe undernutrition	1.12	0.54 – 2.3	0.768
Severe undernutrition	2.83	1.34 – 5.99	0.007
Age <70 years	ref		
Age 70-80	0.31	0.09 – 1.03	0.056
Age 80-90	0.35	0.11 – 1.09	0.069
Age >90	0.57	0.17 – 1.98	0.38
Platelet count in Giga/L	1	1 – 1.01	0.009
Plasmatic zinc	0.92	0.85 – 1	0.055
Bleeding history	3.49	1.63 – 7.51	0.001
Low risk, Beyth score	0.42	0.04 – 4.61	0.48
High risk, Beyth score	1.58	0.68 – 3.64	0.286

Abbreviations : CI, confidence interval ; ref, reference.

Figure 1. Receiver operating characteristic curve from final multivariate analysis



	Observation	AUC	SD	95% CI
Multivariable model	265	0.7238	0.0349	0.655 – 0.792
Undernutrition status	265	0.6208	0.0355	0.551 – 0.690
NRI score	265	0.6305	0.0361	0.559 – 0.701
PINI score	265	0.5352	0.0372	0.462 – 0.608

Abbreviations: AUC, area under curve; SD, Standard Deviation; CI, confidence interval; NRI, nutritional risk index; PINI, Pronostic Inflammatory and Nutritional Index

