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Coagulation

Vitamin K deficiency in critical ill patients; a prospective observational study

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ABSTRACT

Background: Vitamin K is a cofactor for proteins involved in cardiovascular health, bone metabolism and cancer. Measuring uncarboxylated prothrombin, also termed as "protein induced by vitamin K absence or antagonism for factor II (PIVKA-II)", has been used to assess vitamin K status. High levels may indicate vitamin K deficiency. The aim of this study was to measure PIVKA-II and prothrombin time (PT-INR) in intensive care (ICU) patients and correlate vitamin K status with mortality. Methods: Ninety-five patients admitted to the ICU had blood samples taken near admission and every third day. In addition to PIVKA-II and PT-INR, critical-care severity scores were computed. Results: The median baseline PIVKA-II was 4.97 μg/L compared to the upper reference of 2.0 μg/L. PIVKA-II further increased at days 3 and 6, (median 7.88 μg/L, $p = .047$ and median 8.14 μg/L, $p = .011$) predominantly in cardiac arrest patients (median 21.4 μg/L, day 3). Conclusion: Intensive care patients have increased PIVKA-II levels at admission, which increases during the ICU stay, especially in cardiac arrest patients. There were no correlations between PIVKA-II and PT-INR, SOFA score or mortality. Further studies are needed to determine why PIVKA-II increases and whether high PIVKA-II levels in ICU patients affect long-term mortality or morbidity.

1. Introduction

Critical illness is associated with increased mortality, both in the acute setting and for several years following discharge from the intensive care unit (ICU) [1]. It was recently shown that impaired vascular and cardiac biomarkers at ICU discharge were independently associated with increased one-year mortality [2]. Furthermore, malnutrition [3] and coagulopathy [4,5] contribute to increased mortality in patients admitted to the ICU.

The micronutrient vitamin K has traditionally been considered mainly involved in haemostasis where it facilitates γ-carboxylation of vitamin K-dependent hepatic clotting factors. However, several vitamin K dependent proteins originating from extra-hepatic tissues have been identified and implicated in a number of potential disease pathways, such as cardiovascular health [6], inflammation [7,8] and osteoporosis [9]. In particular, research has focused on cardiovascular health as studies have shown that patients treated with vitamin K antagonists (VKA) tend to have increased vascular calcification compared to patients not on VKA treatment [10]. Several clinical trials investigating whether supplementation with vitamin K improves vascular health are ongoing [11]. It is not clear if a subclinical vitamin K deficiency affects the short- or long-term prognosis of critically ill patients [12].

The protein induced by vitamin K absence or antagonism for factor II (PIVKA-II) is a measure of undercarboxylated prothrombin and reflects hepatic vitamin K status [13]. The prothrombin time (PT-INR) is the gold standard in coagulation assays. Given that PT-INR is not prolonged until prothrombin levels are reduced by at least 50% [14] the PIKVA-II assay has higher sensitivity than PT-INR assays in detecting subclinical vitamin K deficiency, with increased PIVKA-II levels [15]. In a study that induced subclinical vitamin K deficiency in healthy subjects by providing them a very low vitamin K_1 diet for 13 days, plasma vitamin K_1 levels decreased to 13–18% of the day one values and PIVKA-II levels increased significantly [16]. This indicates that malnutrition can drastically alter vitamin K status over a short period of time.

The primary aim of the present study was to investigate whether high PIVKA-II levels are present and/or occurs during the ICU stay.

Abbreviations: APTT, activated partial thromboplastin time; EMR, expected mortality rate; PIVKA-II, protein induced by vitamin K absence or antagonism for factor II; PT-INR, prothrombin time; MGP, matrix Gla protein; SAPS3, simplified acute physiology score; VKA, vitamin K antagonists; VKOR, vitamin K epoxide reductase; VKORC1L1, vitamin K epoxide reductase complex subunit 1-like 1.

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Secondly, we assessed the correlation between PIVKA-II with PT-INR and mortality.

2. Materials and methods

2.1. Study design

The study was approved by the regional ethical review board in Lund (DNR 2014/916 and 2010/482). Patients admitted to the general ICU at a tertiary university hospital or cared for in the postoperative unit at the same hospital, over 18 years of age were eligible for inclusion. The inclusion period was July to December 2011. Samples were taken during office hours. Patients were treated according to standard of care at the ICU, including nutrition regime with 15–25 kcal/kg/day preferable through enteral route but with addition of parenteral administration when the enteral route was insufficient. Patients were stratified by diagnosis to enable subgroup analysis in the heterogeneous ICU population. Warfarin-treated individuals were classified as a separate subgroup, irrespective of the diagnosis, as VKA affects both routine coagulation assays and PIVKA-II levels [17]. Other subgroups were cardiac arrest, trauma and sepsis, respiratory insufficiency, surgical, postoperative and other. The other subgroup comprised of patients with conditions that could not be classified under any other group, and were not frequent enough to form a subgroup of its own (>5 patients). The difference between the surgical and post-operative subgroup were their post-operative level of care. Patients in the surgical subgroup remained in the ICU > 24 h after surgery whereas postoperative patients were discharged ≤24 h after surgery. PIVKA-II, PT-INR and the sequential organ failure assessment (SOFA) score were sampled near admission, and then every third day until four samples were obtained, or until the patient was discharged or deceased. The expected mortality rate (EMR) calibrated for Swedish ICUs was computed using the simplified acute physiology score (SAPS3) using the formula $EMR = exp(-32{,}06302 + \ln(\text{SAPS 3 score} + 10{,}34{,}171) * 7{,}199{,}704)/(1 + exp(-32{,}06302 + ln(\text{SAPS 3 score} + 10{,}34{,}171) * 7{,}199{,}704))$ [18]. The exclusion criteria were known bleeding disorders and hepatocellular carcinoma.

2.2. Blood sampling and laboratory analyses

Venous blood was sampled into citrated tubes (BD Vacutainer, 2.7 mL, 0.109 M) for routine PT-INR analysis. The samples were immediately centrifuged at 2000 rpm for 20 min to obtain the plasma fraction and plasma was stored at −80 °C until further analysis.

An analysis of the routine PT-INR was conducted using the Owren method with a combined thromboplastin reagent (Owren PT, Medirox, Sweden) and calibrated using reference samples with certified international normalized ratios (INRs) from Equalis (Uppsala, Sweden). Plasma was analysed with a Sysmex Ca-5100 automated coagulation analyser. The reference range for the PT-INR was defined as 0.9–1.2, with a coefficient of variation of <5%.

An analysis of plasma PIVKA-II levels was performed using an Asserachrom® PIVKA-II kit (Stago, Asnieres-sur-Seine, France). This is an ELISA-based technique where monoclonal antibodies detect abnormal undercarboxylated prothrombin. The upper reference limit was set by the manufacturer to 2.0 μg/L. This reference range is supported by a study of 263 healthy subjects aged 18–85 years who demonstrated mean PIVKA-II levels of 1.58 μg/L with no significant age variation [19]. At each sampling time, PIVKA-II was analysed in duplicate, and the mean results were expressed as μg/L.

2.3. Statistics

Data was processed using IBM SPSS for Windows, version 24.0 (SPSS Inc., Chicago, Ill., USA). Variables were non-parametric (Gaussian distribution not assumed). Change over time was analysed using the Wilcoxon signed rank test for paired samples. The Spearman rank correlation method was used to find correlations between variables. The statistical significance level was set to $p < .05$.

3. Results

3.1. Patient characteristics

Ninety-five patients were included in the study, 35 females and 60 males, with a median age of 66 years. Patients were evaluated as one cohort and then divided into subgroups depending on the diagnosis at ICU-admission. The subgroups consisted of cardiac arrest (n = 10), trauma (n = 9), sepsis (n = 19), respiratory insufficiency (n = 13), surgical (n = 10), postoperative (n = 23) and other (n = 7), warfarin-treated patients (n = 4). The diagnoses in the "other" subgroup was kidney failure, liver bleeding and circulatory insufficiency. Eight patients had conditions affecting the liver. These included alcoholic liver cirrhosis (n = 1), colorectal cancer with liver metastases (n = 2), liver resection due to echinococcus cyst (n = 1), traumatic liver bleeds (n = 2), liver abscess with bleeding (n = 1) and septic shock with liver and kidney failure (n = 1).

The patient characteristics are summarized in Table 1.

3.2. Baseline

Median PIVKA-II at baseline was 4.97 μg/L for patients not on VKA treatment and 73.4 μg/L for warfarin-treated patients. Baseline PIVKA-II data (all patients included) are shown in Fig. 1. At baseline, the median EMR was 29.9%, the median PT-INR was 1.3 and the median SOFA score was 7. The SOFA scores and EMR were not sampled in postoperative patients. Patients stayed at the ICU for a median of four days. Baseline values of each subgroup are shown in Table 2. Outliers were included in the analyses. Outliers, together with respective clinical data, are summarized in supplementary file 1.

3.3. Changes over time

Two or more consecutive PIVKA-II values were available in 52 patients. A significant increase was found when comparing PIVKA-II at baseline and at consecutive sampling ($p = .047$). Median PIVKA-II at second sampling was 7.88 μg/L for the patients not on VKA treatment and 38.3 μg/L for warfarin-treated patients. Changes in PIVKA-II between the first and second sampling are shown in Fig. 2. A subgroup analysis revealed that cardiac arrest patients demonstrated the largest increase in PIVKA-II, with a median value at the second sampling of 21.40 μg/L (median delta value 18.27 μg/L). In decreasing order, the respiratory insufficiency subgroup had a PIVKA-II median value of 9.34 μg/L (median delta value 2.07 μg/L), trauma had a value of 7.09 μg/L

Table 1
Patient characteristics expressed as median (range).

n	95	
Gender	35 female/60 male	
Age	66 years (18–92)	
Diagnosis[a]	Cardiac arrest	(10)
	Trauma	(9)
	Sepsis	(19)
	Respiratory insufficiency	(13)
	Surgical	(10)
	Postoperative	(23)
	Other	(7)
	Warfarin-treated	(4)
Baseline values	PIVKA-II	5.18 μg/L (0.003–240.2)
	PT-INR	1.3 (0.9–2.4)
	SOFA score	7 (0–16)
	EMR	29.9% (0.4–85.8)

[a] Some patients had more than one diagnosis but are grouped by the main diagnosis only.

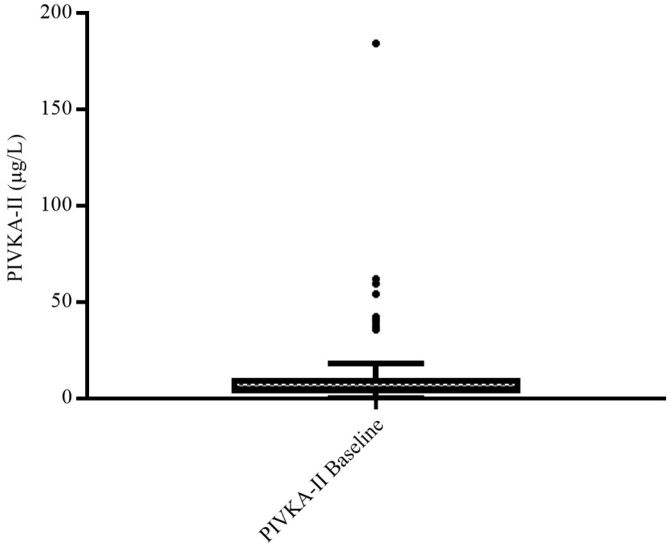

Fig. 1. Boxplot of the baseline PIVKA-II values. n = 91. Patients treated with vitamin K antagonists excluded. Outliers are marked with a circle.

(median delta value 1.45 μg/L), sepsis 5.26 μg/L (median delta value 1.93 μg/L) and surgical 4.41 μg/L (median delta value 0.94 μg/L). The only subgroups in which the PIVKA-II values didn't further increase were in the warfarin-treated patients, who had a median value of 38.3 μg/L at second sampling (median delta value −1.6 μg/L) and the other subgroup who had a median value of 7.01 μg/L (median delta value 2.24 μg/L).

At day 6, twenty-five patients were still being treated in the ICU and were sampled a third time. In those patients, PIVKA-II continued to increase when comparing with either the baseline or second sampling with third sampling ($p = .011$ and $p = .025$, respectively). In cardiac arrest patients, who demonstrated the most drastic increase in PIVKA-II, only one patient was available for the third sampling analysis. This patient's PIVKA-II level continued to increase from 0.49 μg/L at the first sampling to 50.4 μg/L at the second sampling to 166.1 μg/L at the third sampling, and this patient passed away after 13 days in the ICU (Fig. 2).

When comparing changes in SOFA score over time, 35 patients had two or more consecutive scores. In these patients, SOFA score decreased when comparing baseline with the second sampling ($p = .014$) indicating less degree of organ dysfunction (Fig. 3). Between the second and third sampling, there were no significant differences in the SOFA scores. There was no significant change in PT-INR when comparing the baseline with the second sampling in the 31 patients available for analysis. No clinically significant bleeding events where recorded.

3.4. Deceased patients

In the present study, 13 patients died in the ICU. Six from the cardiac arrest subgroup, one from the respiratory insufficiency subgroup and six from the sepsis group. All patients, except one, had a baseline PIVKA-II above the reference range, with a median value of 4.34 μg/L, which further increased in six out of the eight patients available for the second sampling. The median PIVKA-II at the second sampling increased to 15.8 μg/L.

The median PT-INR at baseline was 1.1, which remained largely unaffected. The median SOFA score was 9 and increased in 50% of patients at the second sampling.

3.5. Correlations

There were no correlations between PIVKA-II and PT-INR or between PIVKA-II and mortality or SOFA score at any time. Baseline correlation analyses included 63 patients as post-operative and warfarin-treated patients were not included and in three patients PT-INR was not sampled.

Table 2
Subgroup characteristics and baseline values expressed as median (range).

Subgroup	Subgroup characteristics at baseline	
Cardiac arrest	n	10
	Gender	2 female/8 male
	Age	68.5 years (29–80)
	PIVKA-II	4.09 μg/L (0.49–8.22)
	PT-INR	1.3 (1.1–2.4)
	SOFA score	8.5 (5–12)
	EMR	41.4% (4.6–60.8)
Trauma	n	9
	Gender	4 female/5 male
	Age	32 years (18–92)
	PIVKA-II	4.35 μg/L (0.003–54.2)
	PT-INR	1.2 (1.1–1.7)
	SOFA score	5 (2–9)
	EMR	5.2% (0.4–48.8)
Sepsis	n	19
	Gender	10 female/9 male
	Age	64 years (20–86)
	PIVKA-II	4.33 μg/L (0.37–59.6)
	PT-INR	1.3 (1–1.8)
	SOFA score	10 (0–16)
	EMR	40.3% (1.8–85.8)
Respiratory insufficiency	n	13
	Gender	4 female/9 male
	Age	68 years (50–80)
	PIVKA-II	4.97 μg/L (2.09–17.5)
	PT-INR	1.2 (1.1–1.4)
	SOFA score	5 (2–9)
	EMR	12.2% (1.4–62.7)
Surgical[a]	n	10
	Gender	3 female/7 male
	Age	64 years (18–81)
	PIVKA-II	5.37 μg/L (0.8–62)
	PT-INR	1.3 (1.1–1.5)
	SOFA score	7 (3−10)
	EMR	34% (11.1–62.7)
Postoperative[b]	n	23
	Gender	9 female/14 male
	Age	69 years (21–84)
	PIVKA-II	5.18 μg/L (0.94–184.4)
	PT-INR	1.2 (0.9–1.6)
	SOFA score	N/A
	EMR	N/A
Other	n	7
	Gender	3 female/4 male
	Age	63 years (22–72)
	PIVKA-II	12.8 μg/L (2.11–18.2)
	PT-INR	1.2 (1–1.4)
	SOFA score	7 (4–14)
	EMR	40.3% (1.6–69.5)
Warfarin-treated	n	4
	Gender	4 male
	Age	70 years (63–76)
	PIVKA-II	73.4 μg/L (13.3–240.2)
	PT-INR	1.25 (1.1–1.5)
	SOFA score	6 (5–7)
	EMR	11.1% (5.2–11.1)

[a] Surgical patients remained in the ICU > 24 h.
[b] Postoperative patients were discharged ≤24 h after surgery.

4. Discussion

To the best of our knowledge, this is the first study to investigate changes in the PIVKA-II in ICU patients. As substantial research suggests that subclinical vitamin K deficiency is widespread and that this leads to dysfunctional Gla proteins, it was of interest to determine how vitamin K status affects critical illness in different patient groups. In the present study we demonstrate that PIVKA-II levels near admission were elevated and further increased during the ICU stay. Interestingly, the

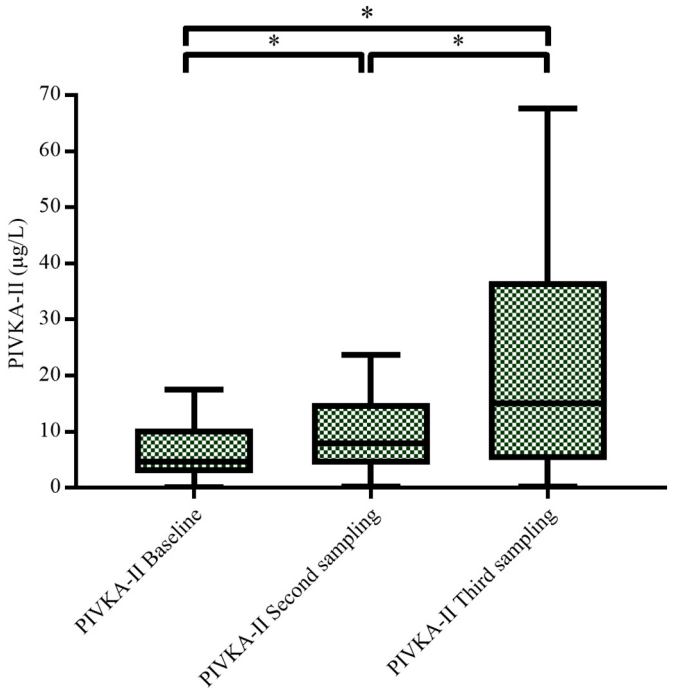

Fig. 2. Boxplot of changes in the PIVKA-II values over time. n = 52 at baseline, n = 52 at second sampling, n = 25 at third sampling. Patients treated with vitamin K antagonists excluded. Outliers were removed from the picture but were included in the calculations. $^{*}p < .05$.

standard PT-INR coagulation assay remained unaffected, due to the insensitivity of this marker for vitamin K status. These findings are in line with findings from previous studies on surgical patients, where increases in the PIVKA-II were demonstrated postoperatively [15,20]. The upper reference limit of PIVKA-II is supported by studies on healthy volunteers, where PIVKA-II also were positively associated with the percentage of uncarboxylated osteocalcin (ucOC) [19], which is another Gla protein used to assess vitamin K status.

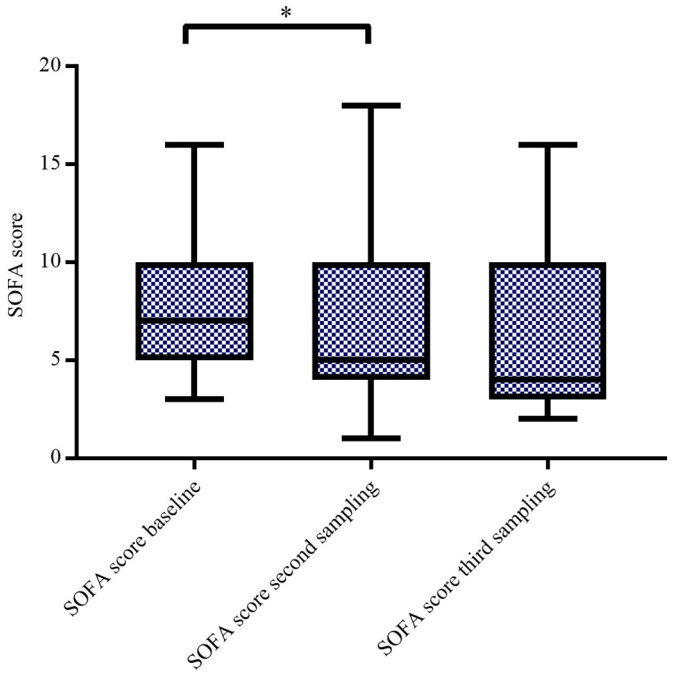

Fig. 3. Boxplot changes in the SOFA score over time. n = 35 at baseline, n = 35 at second sampling, n = 17 at third sampling. Outliers were removed from the picture but were included in the calculations. $^{*}p < .05$.

The increase in PIVKA-II may represent several things. As PIVKA-II is inversely correlated to hepatic vitamin K status an increase in PIVKA-II might reflect exhaustion of hepatic vitamin K stores. The catabolic state promoted by severe illness could lead to a relative vitamin K deficiency with a larger fraction of uncarboxylated prothrombin as a result. It is also possible that the increase in PIVKA-II is a marker for coagulation abnormalities or inflammatory response. However, a previous perioperative study indicate that factor II does not act as an acute phase reactant and also failed to demonstrate any correlation between PIVKA-II and inflammatory marker C-reactive protein (CRP) [21]. Many patients in the ICU are treated with antibiotics, both due to infections and as perioperative prophylaxis. Antibiotics interfere with gut bacterial flora and might therefore affect vitamin K status by depleting menaquinone-synthesizing species. However, in previous work the contribution of gut bacteria to vitamin K status has been considered less important [22].

In cardiac arrest patients, the increase in PIVKA-II measurements between the first and second sampling was most pronounced, perhaps indicating that this subset of critically ill patients is at risk for developing a more severe subclinical vitamin K deficiency or reflecting some other pathophysiological process associated with cardiac arrest. In a recent large prospective study PIVKA-II levels were associated with the incidence of ischemic cardiovascular disease [23]. Perhaps the combination of poor vitamin K status and a systemic post-resuscitation response [24] led to the tangible increase in PIVKA-II demonstrated in cardiac arrest patients. Similar increases were also seen for some patients with sepsis, which is also a condition known to promote coagulation abnormalities, but it was not confirmed on a group level. The involvement of vitamin K and matrix Gla-protein (MGP) in cardiovascular health has gained substantial interest in recent years. Several clinical trials investigating whether vitamin K supplementation might improve vascular health are on-going [11]. A recent clinical trial demonstrated improved arterial stiffness in renal transplant recipients after 8 weeks of vitamin K supplementation [25] and authors suggested that vitamin K status might be a modifiable risk factor for cardiovascular disease. Whether the increase in PIVKA-II solely represents deterioration in vitamin K and whether it affects long-term outcome merits further research. It may be of value to identify at-risk patients and initiate vitamin K supplementation.

Some patients had markedly elevated PIVKA-II levels at baseline. In addition to VKA treatment, which halts the recycling of vitamin K and thereby diminishes prothrombin γ-carboxylation, other factors have been identified as causative agents for the increased PIVKA-II concentrations. These included suspected alcoholic liver disease [26], bariatric surgery [27] and cholangiocarcinoma [28]. The remaining patients with significantly deviating PIVKA-II measurements were admitted to the ICU due to trauma, severe sepsis or septic shock where no previous studies are available to use for a comparative analysis. However, in a study investigating perioperative changes in PIVKA-II, increased levels both before and after surgery were seen in septic patients [15]. The patients who underwent severe trauma were largely previously healthy and still displayed increased PIVKA-II levels. This indicates that the elevated PIVKA-II in this subgroup may be dependent on trauma specific conditions such as haemorrhage or post-traumatic systemic inflammation. In addition to the deviating PIVKA-II levels at baseline, there was a gradually increasing dispersion of PIVKA-II measures over time. This might be due to healthier patients being discharged from the ICU while those remaining for second and third sampling had not yet improved or were deteriorating.

At baseline, the PIVKA-II did not correlate with PT-INR, SOFA score or mortality. Also, no correlation was demonstrated between mortality and delta changes in the PIVKA-II during the ICU stay. This may be due to lack of power since only 63 patients were included in the baseline correlation analyses or may also be due to lack of correlation. Future studies with larger cohorts are needed to unravel the correlation between PIVKA-II and SOFA score and mortality.

We recognize the limitations of the present study including that follow-up blood samples could only be taken in 52 patients mainly due to short length of hospital stay. Furthermore, it could have been of interest to correlate the PIVKA-II with several nutritional markers, such as prealbumin, albumin, creatinine as well as to investigate whether the amount of pre- and intra-hospital nutrition and route of administration affects PIVKA-II levels or patient outcomes. Including markers of vitamin K status more specific for the vascular wall or bone, i.e. measurement of the carboxylation degree of MGP or OC, could have shed light on the consequences of vitamin K deficiency related to cardiovascular disease. Using a combination of biomarkers could also more accurately estimate vitamin K status and help clarify whether the increase in PIVKA-II solely represents vitamin K deficiency or if other pathophysiological processes may affect PIVKA-II levels during critical illness.

5. Conclusions

Patients submitted to the intensive care have elevated PIVKA-II levels, which further increases during the ICU stay, especially in cardiac arrest patients. Further studies are needed to determine what causes the PIVKA-II increase and whether vitamin K deficiency in critically ill patients may affect long-term mortality or morbidity.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.022.

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