Vitamin K is frequently administered in cirrhotic patients to correct their coagulopathy, but evidence for such practice is lacking. We aimed to assess whether vitamin K administration increases the levels of the vitamin K-dependent factor VII (FVII), protein C, and protein S in patients with different stages of liver dysfunction. Eighty-nine patients were recruited into four groups: group 1 [hepatitis B virus (HBV) inactive carriers, \( n = 23 \)]; group 2 [chronic HBV and hepatitis C virus (HCV) hepatitis, \( n = 21 \)]; group 3 (cirrhosis, \( n = 24 \)); group 4 (hepatocellular carcinoma, \( n = 21 \)); and a healthy control group (\( n = 39 \)). A single dose of 10 mg of vitamin K1 was administered subcutaneously to all patients. Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, FVII, protein C, total and free protein S, and proteins induced by vitamin K absence (PIVKA)-II (des-γ-carboxy prothrombin) were measured at baseline and 72 h after vitamin K administration. There was progressive increment in baseline PIVKA-II, and decrements in fibrinogen, FVII, protein C, and protein S across study groups (\( P < 0.0001 \)). Compared to baseline, vitamin K administration did not affect the measured parameters, whereas TT showed no reduction in any of the groups. Protein C levels declined in group 2, whereas FVII, total and free protein S did not increase in any group, for all parameters. Vitamin K therapy does not cause significant improvements in the majority of coagulation parameters and hence does not seem to be routinely indicated in patients with liver disease. Blood Coagul Fibrinolysis 24:10–17 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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The coagulopathy of liver disease: does vitamin K help?

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Introduction

The liver plays a key role in blood coagulation, being the site of synthesis of almost all coagulation factors and inhibitors [1,2]. In addition to synthesis, the hepatic reticuloendothelial system is also involved in the clearance of activated coagulation factors as well as enzyme–inhibitor complexes [2,3]. Thus, coagulation abnormality is a predictable feature of acute as well as chronic liver disease [4].

One of the factors implicated in the pathogenesis of the coagulopathy of liver disease is vitamin K deficiency. Vitamin K occupies a central role in the relationship between the liver and the coagulation system since it is required for the synthesis of functionally active forms of a number of coagulation factors and inhibitors by the liver, including prothrombin, factor VII (FVII), FXI, FX, protein C, and protein S [5]. Its role lies in promoting the carboxylation of certain glutamic acid residues on these vitamin K-dependent (VKD) proteins to γ-carboxyglutamatic acid (Gla), rendering them capable of interacting with calcium ions, which in turn is an essential step for protein-membrane interaction and consequently effective hemostatic function [6–8]. Vitamin K deficiency or antagonism, with the subsequent impairment in γ-carboxylation, will result in the production of under-carboxylated precursors of these proteins, known as ‘proteins induced by vitamin K absence (PIVKA)’, which are functionally inactive [8,9].

In clinical settings, vitamin K deficiency is usually assessed by measuring the prothrombin time (PT) which is prolonged in a wide spectrum of liver diseases [10,11]. Apart from being an indirect measurement of vitamin K status, the PT is also insensitive (since it is only prolonged when the drop in level of coagulation factors approaches 30–40%) and nonspecific, being prolonged even in deficiency of non-VKD factors [2,10,12]. Alternatively, the vitamin K status in the body can be assessed by a better method, that is measuring PIVKA levels, which provide a more sensitive and specific means for the evaluation of vitamin K deficiency [5,10,13].

Despite the lack of evidence supporting the efficacy of vitamin K in correcting the coagulopathy of liver disease, vitamin K administration remains a part of the management of many patients with cirrhosis and end-stage liver disease (ESLD) who demonstrate abnormalities in their coagulation parameters. It is understandable that vitamin K administration can correct the coagulopathy in biliary
Enrolment of study groups

Patients and methods

Enrolment of study groups

A total of 89 patients were prospectively recruited from the hepatology clinics and medical wards of King Khalid University Hospital and Riyadh Military Hospital over a period of 12 months (January to December 2007), and basic demographic data were recorded for all patients. Their ages ranged from 19 to 100 years (mean 49.4 ± 17.4 years) and 58 (65.2%) were men. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review boards of both centers. Informed consent was obtained from all enrolled patients.

Study design and patients

Patients were recruited into four groups. Group 1 (n = 23) consisted of inactive hepatitis B virus (HBV) carriers; the diagnosis was based on the presence of hepatitis B surface antigen (HBsAg) (>6 months) in the serum with persistently normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (measured at least twice 6 months apart) and a HBV DNA level below 20 000 IU/ml. Group 2 (n = 21) recruited patients with chronic viral hepatitis diagnosed by the demonstration of a positive HBsAg and HBV DNA at least 20 000 IU/ml or positive anti-hepatitis C virus (HCV) antibody (ELISA version 4.0; Murex Biotech S.A., South Africa) and detectable HCV RNA by PCR (Amplicor; Roche Diagnostics, New Jersey, USA), with persistently elevated ALT (above the upper limit of normal) and no laboratory or radiological features of cirrhosis (including 12 unselected patients with evaluable liver biopsy confirming chronic hepatitis). Group 3 (n = 24) consisted of patients with cirrhosis (including five patients with evaluable liver biopsy showing cirrhosis). Group 4 (n = 21) recruited patients with hepatocellular carcinoma (HCC).

The diagnosis of cirrhosis was based on liver biopsy or the presence of at least two of the following: platelet count less than 90 000/l, radiological [ultrasonography or computed tomography (CT)] evidence of cirrhosis, or esophageal varices (demonstrated by endoscopy); and at least two signs of liver dysfunction: albumin level below 30 g/l, international normalized ratio (INR) at least 1.3, or bilirubin level above 35 μmol/l [14,15]. All participants had screening abdominal ultrasonography at the time of recruitment into the study. The ultrasonography was performed and interpreted by trained radiographers according to a standardized protocol, and the records reviewed by the investigators. Cirrhosis was inferred based on the appearance of the liver surface, liver parenchymal texture, portal vein size, splenic size, presence of ascites, and varicose veins in the portal and perisplenic area. Additionally, all patients with an α-fetoprotein (AFP) above 200 ng/l (or a persistently rising AFP) or with high clinical suspicion of HCC underwent further investigations including a CT and/or MRI of the liver. The diagnosis of HCC was based upon published guidelines for the diagnosis and management of HCC [16].

Enhancement of a liver lesion during the arterial phase and contrast washout during the portal phase, in patients with background cirrhosis was considered diagnostic of HCC. Trucut biopsy or fine needle aspiration was obtained only when considerable doubt existed after imaging studies and AFP tests.

Vitamin K was administered to all patients as a single dose (10 mg vitamin K1; KonakionMM; Roche Ltd, Basel, Switzerland) given subcutaneously in the upper part of the arm. All patients were seen at baseline and 3 days after vitamin K administration by the study investigators.

The control group (n = 39) consisted of healthy individuals who were recruited randomly from blood donors, academic staff, and volunteers from the general public. Their ages ranged between 19 and 70 years (mean 37.6 ± 9.7 years), and 26 (66.7%) were men.

General exclusion criteria for all groups included history of bleeding or thrombotic disorder, history of renal disease, diabetes mellitus, ongoing or recent pregnancy in the preceding 6 months, history of transfusion of blood products in the preceding 1 month, or the use of any of the following medications: heparin, warfarin, immunomodulatory drugs such as steroids, NSAIDs, antiviral therapy in the preceding 6 months, and vitamin K, and/or multivitamins. Patients with chronic cholestatic liver diseases or those with recent episodes of cholangitis within the preceding 6 months were excluded.

Blood collection and processing

Blood samples were collected for each patient on two occasions: the first, before vitamin K administration and the second sample was drawn 72 h following vitamin K administration. The usual precautions of selecting an easily accessible vein in the antecubital fossa and using the minimum of venous stasis were observed. 9.5 ml of blood were collected by venipuncture directly into vacutainer tubes containing 0.5 ml sodium citrate (3.8%,...
Blood samples were transported immediately to the Coagulation Research Laboratory, Physiology Department of King Khalid University Hospital. The citrated blood sample tubes were centrifuged at 3000 r.p.m. (1000g) for 15 min in a refrigerated (4–6°C) centrifuge (Juan, France). Platelet-poor plasma was separated using plastic pipettes, and aliquots of plasma were immediately stored at ~80°C until analysis, in batches, at a later date. Prior to performing the assays, plasma specimens were thawed at 37°C for 15 min.

**Laboratory assays**

The following parameters were measured using kits supplied by Diagnostica Stago (9, rue des Frères Chausson, 92600 Asnières sur Seine, France) and according to the manufacturer’s instructions: FVII: using immunodepleted plasma for FVII (STA-Deficient VII) and was performed by multiple dilution parallel line bioassay using rabbit brain-derived thromboplastin; the coefficient of variation of FVII was 4%; protein C by colorimetric assay (Asserachrom total and free); coefficient of variation less than 5%; total and free protein S; coefficient variation below 5%; PIVKA-II by enzyme immunoassay (Asserachrom PIVKA-II).

The coagulation screening tests, namely activated partial thromboplastin time (APTT; PPT-A, Diagnostica Stago), PT (Neoplastine, Diagnostica Stago), and thrombin time (TT; Parke-Davis Topical Bovine Thrombin, Ann Arbor, MI, USA) were performed by the conventional methods and the clotting times were registered by an optical coagulation system (ST-ART; Diagnostica Stago). Fibrinogen assay was performed by the turbidometric method of Ellis and Stransky [17] (coefficient of variation 6–8%).

**Statistical analysis**

To facilitate comparisons, the results of the coagulation screening tests (PT, APTT, and TT) are expressed as percentage (%) of the laboratory-pooled control plasma (which represents 100% in all assays). The descriptive statistics (mean and SD) were used to describe the outcome variables. The Student’s t-test for dependent samples (pre and post vitamin K) was used to compare the mean values of continuous variables in relation to the categorical variables (two groups). The one-way analysis of variance (ANOVA) was used to compare the mean values of continuous outcome variables across more than two groups. Duncan’s multiple range test was used to perform the pair-wise comparison. Karl Pearson correlation coefficient and Spearman’s correlation coefficient were used to quantify the relationship between two continuous variables. A P value of less than 0.05 was taken as statistically significant. Statistical package for social sciences (SPSS, version 16.0; Chicago, Illinois, USA) was used for data analysis.

**Results**

Overall, 89 patients were included of whom 57 (64%) were men. The mean age of the patients increased across increasing severity of liver disease (Table 1; $P<0.0001$). The mean BMI was lower in the HCC patients as compared to other groups but did not reach statistical significance ($P=0.348$). By design, serum AST, ALT, γ-glutamyl transpeptidase (GGT), and bilirubin levels were significantly higher in groups 2–4 compared to controls and group 1 ($P<0.05$ for all; Table 1).

**Coagulation screening tests**

To minimize the day-to-day variation in the levels of the coagulation screening tests and to facilitate comparisons, the results of the individual measurements are expressed as percentage of control pooled plasma. The PT showed a

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**Table 1** Baseline patient characteristics of the four study groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (n = 39)</th>
<th>Group 1 (n = 23)</th>
<th>Group 2 (n = 21)</th>
<th>Group 3 (n = 24)</th>
<th>Group 4 (n = 21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.6 ± 9.7</td>
<td>38.0 ± 10.8</td>
<td>38.6 ± 16.2</td>
<td>56.2 ± 9.3</td>
<td>65.6 ± 15.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>26 (66.7)</td>
<td>13 (56.5)</td>
<td>17 (80.6)</td>
<td>14 (58.3)</td>
<td>13 (61.9)</td>
<td>0.470</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>26 (66.7)</td>
<td>13 (56.5)</td>
<td>17 (80.6)</td>
<td>14 (58.3)</td>
<td>13 (61.9)</td>
<td>0.470</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 ± 7.7</td>
<td>28.7 ± 6.3</td>
<td>26.5 ± 5.7</td>
<td>27.8 ± 6.6</td>
<td>22.7 ± 6.5</td>
<td>0.348</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>28.9 ± 9.1</td>
<td>24.4 ± 29.5</td>
<td>81.8 ± 54.6</td>
<td>53.7 ± 66.1</td>
<td>73.9 ± 78.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>26.1 ± 11.7</td>
<td>25.3 ± 13.1</td>
<td>52.1 ± 32.1</td>
<td>81.4 ± 84.2</td>
<td>91.4 ± 52.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GGT (U/l)</td>
<td>29.4 ± 15.3</td>
<td>27.4 ± 14.3</td>
<td>75.8 ± 49.7</td>
<td>89.5 ± 106.1</td>
<td>163.0 ± 247.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>9.5 ± 5.1</td>
<td>9.2 ± 3.2</td>
<td>14.9 ± 8.7</td>
<td>49.8 ± 54.3</td>
<td>37.6 ± 42.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin (mg/l)</td>
<td>42.3 ± 4.7</td>
<td>41.0 ± 9.0</td>
<td>40.5 ± 5.1</td>
<td>32.1 ± 6.9</td>
<td>28.9 ± 6.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PT (s)</td>
<td>110.0 ± 10.6</td>
<td>118.8 ± 19.1</td>
<td>124.1 ± 11.0</td>
<td>166.3 ± 53.5</td>
<td>151.7 ± 41.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>120.0 ± 24.2</td>
<td>118.9 ± 17.0</td>
<td>118.9 ± 10.2</td>
<td>146.1 ± 28.9</td>
<td>128.7 ± 19.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombin time (%)</td>
<td>107.7 ± 15.0</td>
<td>121.2 ± 27.7</td>
<td>120.0 ± 35.5</td>
<td>136.0 ± 19.9</td>
<td>138.1 ± 26.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen (mg/l)</td>
<td>307.1 ± 117.5</td>
<td>350.0 ± 146.6</td>
<td>320.0 ± 130.8</td>
<td>183.8 ± 113.3</td>
<td>288.3 ± 233.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>92.9 ± 26.3</td>
<td>91.4 ± 39.6</td>
<td>75.3 ± 26.0</td>
<td>57.2 ± 43.6</td>
<td>53.2 ± 33.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>110.4 ± 20.1</td>
<td>91.2 ± 30.7</td>
<td>85.8 ± 25.2</td>
<td>40.1 ± 24.0</td>
<td>43.4 ± 26.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protein S (%)</td>
<td>301.7 ± 117.5</td>
<td>350.0 ± 146.6</td>
<td>320.0 ± 130.8</td>
<td>183.8 ± 113.3</td>
<td>288.3 ± 233.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Group 1, inactive hepatitis B carriers; group 2, chronic hepatitis B and C; group 3, cirrhosis; group 4, hepatocellular carcinoma. ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; PIVKA, proteins induced by vitamin K absence; PT, prothrombin time.
significant prolongation in both the cirrhosis (166.3 ± 53.5) and HCC (151.7 ± 41.4) groups when compared to controls (110.0 ± 10.6; P < 0.0001), whereas the APTT was prolonged only in the cirrhosis group (146.1 ± 28.9) when compared to controls (120.0 ± 24.2; P < 0.0001). Similarly, when compared to controls (101.1 ± 13.5), TT was prolonged in cirrhosis (132.7 ± 17.9; P = 0.001) and HCC (138.1 ± 26.2; P < 0.0001) groups. Neither the HBV-inactive carriers nor the chronic hepatitis groups showed any significant difference in their PT, APTT, or TT when compared to controls (P > 0.05 for all comparisons).

Upon vitamin K administration, the PT (166.3 ± 53.5 vs. 152.8 ± 39.4; P = 0.016) and APTT (146.1 ± 28.9 vs. 132.5 ± 35.5; P = 0.047) displayed a significant reduction only in the cirrhosis group when compared to their baseline levels, whereas in the other groups no reduction was observed (P > 0.05 for all; Fig. 1). The TT showed no difference in its level post vitamin K administration when compared to its baseline level in any of the groups (P > 0.05 for all; Fig. 1).

**Coagulation factors**

Only the cirrhosis group had a significantly lower mean baseline fibrinogen level (183.8 ± 113.3 mg) when compared to controls (307.1 ± 117.5 mg; P < 0.0001), with levels being not significantly lower in relation to or between other groups (P > 0.05). FVII was significantly lower in the cirrhosis (57.2 ± 43.6) and HCC (53.2 ± 23.3) groups, when compared to controls (92.9 ± 26.3; P = 0.004 and P = 0.001, respectively) or to HBV-inactive carriers (91.4 ± 39.6; P = 0.006 and P = 0.002, respectively). Administration of vitamin K had no effect on the levels of fibrinogen and FVII levels when compared to their baseline levels in any of the groups (P > 0.05 for all; Fig. 2).

**Natural coagulation inhibitors**

**Protein C**

The mean baseline protein C level showed significant progressive decrements with increasing severity of liver disease (Table 1; P < 0.0001). The levels of protein C in cirrhosis (40.1 ± 24.0) and HCC (43.4 ± 26.2) were significantly lower than those of healthy controls (110.4 ± 20.1; P < 0.0001 for both), HBV-inactive carriers (91.2 ± 30.7; P < 0.0001 for both), and chronic hepatitis (85.6 ± 25.2; P < 0.0001 for both). The protein C levels in the chronic hepatitis group showed a significant reduction from baseline (85.6 ± 25.2) upon vitamin K administration (80.7 ± 23.0; P = 0.010), whereas these levels did not change significantly in the remaining three groups (P > 0.05 for all; Fig. 3).

**Total and free protein S**

The total protein S was significantly lower in the cirrhosis (50.1 ± 24.1; P < 0.0001) as well as the HCC (59.7 ± 27.2; P < 0.0001) groups in comparison to the controls (89.4 ± 10.8; Table 1), HBV-inactive carriers (77.2 ± 21.5), and chronic hepatitis (79.6 ± 17.6) groups. Similarly, free protein S was lower in the cirrhosis (47.5 ± 10.7) and HCC (55.1 ± 16.1) groups in comparison to the controls (68.2 ± 12.1; P < 0.0001 for both), HBV-inactive carriers (62.8 ± 14.7; P = 0.001 and P = 0.013, respectively), and chronic hepatitis (64.7 ± 19.6; P = 0.001 and P = 0.006, respectively; Table 1). The total and free protein S did not differ significantly in their levels.
baseline and post vitamin K levels in any of the groups ($P > 0.05$ for all; Fig. 3).

**PIVKA-II**

The mean baseline PIVKA-II levels showed significant progressive increments with increasing severity of liver disease (Table 1; $P < 0.0001$). Baseline serum PIVKA-II levels were significantly higher in the HCC (46.8 ± 82.4 ng/ml; $P < 0.0001$) group when compared to controls (1.1 ± 0.9 ng/ml; $P < 0.0001$) and all study groups ($P < 0.0001$ for all), whereas there were no significant differences between other groups ($P > 0.05$ for all). A decrease in PIVKA-II levels was seen upon vitamin K administration in both the chronic hepatitis (1.8 ± 2.1 vs. 0.71 ± 0.58 ng/ml; $P = 0.022$) and the cirrhosis groups (3.1 ± 5.2 vs. 0.93 ± 1.1 ng/ml; $P = 0.024$) but not in the HCC group (35.6 ± 80.3; $P = 0.187$; data not shown).

**Discussion**

The hemostatic disturbances that occur in patients with liver disease are complex and multifactorial [2,3,17]. Diminished plasma levels of coagulation factors, particularly the vitamin K-dependent clotting FVII and the natural anticoagulants, protein C and protein S, were reported in advanced liver disease [1,18–24]. In the current study we confirm the early observations of the reduced levels of FVII, protein S, and protein C in advanced stages of liver disease, namely, cirrhosis and HCC, which are attributed partly to decreased synthesis of these proteins by the malfunctioning hepatocytes, and
in part to consumption during a process of intravascular coagulation, that may complicate ESLD [18,23–25]. Chronic liver disease has traditionally been considered as an acquired bleeding disease. However, the understanding of coagulopathy of chronic liver disease has gained new insights, shifting the concept of chronic liver disease as being a purely acquired bleeding disorder to the possibility that it can also be complicated by thrombotic complications [26,27]. This is based on direct evidence that plasma from cirrhotic patients could generate similar, or even greater amounts of thrombin than plasma from healthy individuals when thrombin generation is measured in the presence of thrombomodulin [27,28].

Other additional and usually overlooked procoagulant changes include very high levels of von Willebrand factor along with reduced levels of ADAMTS 13 that enhances platelet adhesion [26]. There is also an increase in the FVIII:protein C ratio which means marked reduction in the ability of the protein C to undertake its inhibitory action on active FVIII:C (aFVIII:C), so-called resistance to activated protein C. Interestingly, this thrombotic tendency which underlies the setting of liver fibrosis raises the possibility of anticoagulation in liver disease as a preventive measure against the progression of liver cirrhosis [27].

Thus, in chronic liver disease, the coagulation mechanism undergoes a complex rebalance in both the procoagulants and anticoagulants [26], which obviously cannot be reflected by measurement of the conventional coagulation screening test, the PT, and APTT [29]. Why some cirrhotic patients bleed lies more with risk factors other than hypocoagulability [26], including hemodynamic alterations subsequent to portal hypertension, endothelial dysfunction, bacterial infection, hepato-renal syndrome, and thrombocytopenia that are common in cirrhosis [26,27]. There is also a clinical implication as to the wisdom of the unrestricted use of plasma infusion to correct the results of conventional coagulation tests in liver patients undergoing invasive procedures [29].

We also raise the question as to the benefits of the common practice of liberal administration of vitamin K in patients with liver disease. The contribution of vitamin K deficiency to the coagulopathy of liver disease is controversial and has not been subjected to scientific scrutiny. Although liver injury per se may not cause vitamin K deficiency, it frequently accompanies liver disease [2]. Many factors contribute to vitamin K deficiency including intra-hepatic and extra-hepatic cholestasis, prolonged oral antibiotic therapy, malnutrition, and malabsorption [3,30]. In addition, 25% of patients with acute liver failure (ALF) were found to have subclinical vitamin K deficiency that may progress to overt deficiency, with raised INR and a bleeding tendency [8].

Vitamin K is frequently prescribed in the management of patients with ESLD who demonstrate abnormalities in their coagulation parameters. Although vitamin K administration can achieve full correction of coagulation parameters in cases of biliary tract disease and gut sterilization by broad-spectrum antibiotics where vitamin K deficiency is the main reason behind the coagulopathy [4], in cases of cirrhosis where there is extensive damage to hepatocytes, the benefit of administering vitamin K to these patients is questionable and the evidence to support this practice is vastly lacking.

This aspect has been clearly demonstrated in our study in which the majority of coagulation and natural anticoagulant parameters were not affected by the administration of vitamin K, whereas only PT and APTT were minimally improved in cirrhotic patients with values that, although statistically significant, are unlikely to have any clinical significance in terms of reduction of the risk of bleeding as the magnitude of the fluctuations observed fell within the intra-assay coefficient of variation of these parameters. Other than it being mild, the improvement noted in the PT and APTT levels was not mirrored by a reciprocal improvement in the other vitamin K-dependent proteins (protein S, FVII, and protein C). In fact, protein C, the only parameter displaying any significant difference, showed a decline, rather than a desired increase in its level after vitamin K administration, thus rendering the change completely irrelevant.

Previous studies have found elevated levels of PIVKA-II in patients with vitamin K deficiency [9,10], which eventually decline upon vitamin K administration [8,31]. The present study demonstrated significantly elevated PIVKA-II levels only in patients with HCC when compared to healthy controls as well as all the liver disease groups. These results are in line with other studies that reported high PIVKA-II levels in patients with HCC and low levels in patients with chronic hepatitis and cirrhosis [32,33]. This is not unexpected since PIVKA-II may be produced by the tumor cells [6]. Failure to demonstrate elevated PIVKA-II levels in chronic hepatitis and cirrhosis suggests that vitamin K deficiency, as such, does not play a major role in the coagulopathy associated with cirrhosis, especially, when there is no associated identifiable risk factor for vitamin K deficiency. In this study, the administration of vitamin K resulted in a mild, but statistically significant, decrease in the PIVKA-II levels in patients with cirrhosis and chronic hepatitis. However, the occurrence of such an improvement when PIVKA-II levels were not significantly different from those of the controls lends little support to the existence of vitamin K deficiency in these patients.

A careful search in the literature identified only two previous studies on the effect of the administration of vitamin K in patients with chronic liver disease. In one study, the administration of vitamin K to cirrhotic


patients who had prolonged PT and elevated levels of undercarboxylated prothrombin did not correct the PT, nor did it cause a decrease in the level of undercarboxylated prothrombin [9]. The second study suggested that impaired synthesis of coagulation proteins, rather than impaired carboxylation, was the main reason behind the coagulopathy that accompanies chronic liver disease, and that vitamin K administration did not cause any improvement in the coagulation parameters [34]. Our study broadly concurs with these findings. Nonetheless, our findings represent a pilot effort to study the effect of vitamin K on the coagulopathy of liver disease, particularly at differentiated levels of hepatic dysfunction. We believe that larger studies in different populations should be undertaken in order to confirm these findings.

One of the shortcomings of this study is that the vitamin K-dependent factors were measured only twice, once prior to vitamin K administration, and 3 days thereafter. Presently, there is no consensus on the optimum time frame to measure these parameters in order to detect changes following the administration of vitamin K. Serial daily testing of patients after vitamin K would have been ideal but would have probably compromised patients’ compliance since the majority of our patients were outpatients. In the absence of previous studies to guide us to the most appropriate day to test after vitamin K administration, we opted to test patients on the third postvitamin K therapy day based on the 3 days it takes the vitamin K antagonist warfarin to lose its effect on the circulating levels of vitamin K-dependent clotting factors. We also opted to administer a single dose of vitamin K, rather than three consecutive doses over 3 days, which in turn is an arbitrary practice without any evidence base. Although three doses could potentially have been more effective, this would have come at the cost of patient compliance and convenience. Additionally, we opted to administer vitamin K subcutaneously rather than intravenously, where the effect is anticipated to be more potent as recommended by the manufacturer and as routinely used in clinical practice. Additionally, previous studies have shown that the effect of intravenous and subcutaneous vitamin K in reversing excessive oral anticoagulation is similar. By serially measuring the INR, Nee et al. [35] demonstrated that the intravenous and subcutaneous routes were equally and maximally efficacious at 72 h after administration. Finally, a minor potential limitation of the study that in theory may have affected the measurement of PT and compromised its results is that the centrifugation of whole blood samples was done at a low temperature, thereby increasing the risk of cold-activating FVII and compromising the validity of these data. This aspect could potentially have impact on the PT results.

In conclusion, the administration of vitamin K to patients with cirrhosis resulted in only very minimal, likely clinically insignificant, improvement in only PT and PTT values with no effect on all other vitamin K-dependent parameters of coagulation and natural anticoagulants, and therefore the use of vitamin K in the management of patients with advanced stages of liver dysfunction seems to be unjustified. Nonetheless, these findings should be carefully assessed against the emerging recent evidence of rebalance in the coagulation system with the possibility that some patients with chronic liver disease may develop venous thromboembolism and that standard thromboprophylaxis may be considered when such patients are exposed to compounding risks of venous thromboembolism, such as prolonged recumbence associated with surgery or injury of the lower limbs, or hospitalization [36]. As such, the administration of vitamin K that increases the procoagulant side of the coagulation balance would seem counter-intuitive.

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Conflicts of interest
There are no conflicts of interest.

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