

# Effect of vitamin K1 on survival of patients with chronic liver failure

## A retrospective cohort study

Zhuang Xiong, MD, PhD<sup>a,e</sup>, Yangyang Liu, MD, PhD<sup>b,e</sup>, Tianying Chang, MS<sup>c,e</sup>, Xiaohao Xu, MS<sup>d,e</sup>, Shaokai Huo, MS<sup>e</sup>, Houbo Deng, MD, PhD<sup>a,e</sup>, Tiejun Liu<sup>a,e</sup>, Yan Leng, MD, PhD<sup>a,e,\*</sup>

### Abstract

The effectiveness of vitamin K1 for the treatment of liver failure has been controversial, and no studies have investigated the effect of vitamin K1 on the risk of death and coagulation function in patients with chronic liver failure. This study aimed to explore the effect of vitamin K1 on death risk and international normalized ratio in patients with chronic liver failure.

From December 2013 to August 2017, this retrospective cohort study screened patients hospitalized for chronic liver failure (n = 80) who received routine treatment. The patients were categorized into the vitamin K1 and control groups according to whether they had received intramuscular injection of vitamin K1 on the basis of conventional treatment. Baseline data were analyzed with  $\chi^2$  test and independent sample *t*-test; the survival curve of 48 weeks was created with Kaplan–Meier estimator. Correlation between death event and vitamin K1, age, sex, albumin (ALB), total bilirubin (TBIL), and alkaline phosphatase (ALP) was determined with the Cox proportional risk regression model.

Fifty-seven Chinese patients were finally included in the analysis. Patients treated with vitamin K1 had a lower risk of death (hazards ratio [HR] 0.37,  $P=0.009$ ) than the control group ( $P=0.006$ ). Men had a higher risk of death (HR 2.97,  $P=0.005$ ). Age, ALB, TBIL, and ALP had a certain correlation with risk of death. Vitamin K1 reduced the international normalized ratio levels [ $P < 0.01$  (95% confidence interval 0.000–0.002)].

Vitamin K1 may reduce the risk of death in patients with chronic liver failure. Male sex, age, ALB, TBIL, and ALP are potential risk factors for increased risk of death in these patients. Based on these findings, vitamin k1 can be used in patients with chronic liver failure. Prospective studies are still needed, however, to validate the role of vitamin K1 in the chronic liver failure.

**Abbreviations:** ALB = albumin, ALP = alkaline phosphatase, TBIL = total bilirubin, ULN = upper limit of normal.

**Keywords:** cholestasis, liver failure: vitamin K1

### 1. Introduction

Chronic liver failure is the base of cirrhosis and causes clinical manifestations such as ascites or hepatic encephalopathy, which is caused by a progressive decline in liver function to chronic liver

function decompensation.<sup>[1,2]</sup> Chronic liver failure is the end stage of liver disease, with the primary laboratory diagnostic criterion of prothrombin activity <40%. Congenital immune system diseases and cytokines play a major role in the

Editor: Chandrasekharan Rajasekharan.

Funding: This work was supported by the Fund of the National Natural Science Foundation of China (No. 81804007), Jilin Science and Technology Department Project (No. 20190304075YY), and Changchun University of Chinese Medicine High-level Talent Fund Project (No. 2018KJ04).

Competing interests: We declare that we have no competing interests.

The authors have no conflicts of interest to disclose.

Patient consent for publication: Obtaining patients' consent was not required, as this manuscript only included anonymized patient information.

Ethics approval: This study is a retrospective study approved by the Ethics Committee of the First Affiliated Hospital to Changchun University of Chinese Medicine.

Provenance and peer review: Not commissioned and externally peer reviewed.

Data sharing statement: No additional data are available. All data from this study are available to all qualified researchers/research groups and to international researchers.

<sup>a</sup> Department of Hepatology, <sup>b</sup> Endocrinology, <sup>c</sup> GCP Department, <sup>d</sup> Research Center of Traditional Chinese Medicine, First Affiliated Hospital to Changchun University of Chinese Medicine, <sup>e</sup> Changchun University of Chinese Medicine, Changchun City, Jilin Province, China.

\* Correspondence: Yan Leng, Department of Hepatology, First Affiliated Hospital to Changchun University of Chinese Medicine, 1478 Gongnong Road, Changchun City, Jilin Province, China (e-mail: 1289021445@qq.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Xiong Z, Liu Y, Chang T, Xu X, Huo S, Deng H, Liu T, Leng Y. Effect of vitamin K1 on survival of patients with chronic liver failure: a retrospective cohort study. *Medicine* 2020;99:13(e19619).

Received: 4 June 2019 / Received in final form: 31 December 2019 / Accepted: 21 February 2020

<http://dx.doi.org/10.1097/MD.00000000000019619>

development of acute liver failure, and microcirculation disorders and portal hypertension are common features of chronic liver disease.<sup>[3]</sup> Although chronic liver failure progresses more slowly than acute liver failure, they remain a major threat to human health, and patients may eventually require liver transplantation. Vitamin K is an essential cofactor for the liver to synthesize factor II, II, VII, X,<sup>[4]</sup> but the effectiveness of vitamin K1 has been controversial in the treatment of liver failure. China's 2012 and 2018 *Guidelines for the Diagnosis and Treatment of Liver Failure*,<sup>[1]</sup> 2011 AASLD "Acute Hepatic Failure Treatment",<sup>[3]</sup> and "EASL clinical practice guidelines on the management of acute (fulminant) liver failure (2017)"<sup>[5]</sup> have mentioned the use of vitamin K, but its advantages and disadvantages in the treatment of hepatic failure and coagulation dysfunction are unclear. In addition, a cochrane systematic review shows that "Until randomised clinical trials are conducted to assess the trade-off between benefits and harms, we cannot recommend or refute the use of vitamin K for upper gastrointestinal bleeding in people with liver diseases."<sup>[6]</sup> Currently, there are no studies that investigated the effect of vitamin K1 on the risk of death and coagulation function in patients with chronic liver failure. This study aimed to explore the effects of vitamin K1 on mortality and international normalized ratio (INR) in patients with chronic liver failure.

## 2. Methods

### 2.1. Design, sample, and criteria for participation

This retrospective cohort study was conducted at the Department of Hepatology, First Affiliated Hospital to Changchun University of Chinese Medicine. Electronic medical records of patients with chronic liver failure were collected from December 2013 to August 2017, and 80 patients were screened. Each patient was followed up for 48 weeks. Patients hospitalized for chronic liver failure who received routine treatment were included in the study. Patients who were not followed up and whose time of death was unclear, those receiving vitamin K1 for < 3 days, and those with severe cardiopulmonary dysfunction or a malignant tumor were excluded. The patients were categorized into the vitamin K1 (n=43) and control (n=14) groups according to whether they had received intramuscular injection of vitamin K1 on the basis of the conventional treatment. The routine treatment was based on the 2012 *Guidelines for the Diagnosis and Treatment of Liver Failure* in China, and the use of vitamin K1 was also based on the guideline of "recommended routine use of vitamin K 5 to 10 mg" and daily intramuscular injection of 10 mg. The selection process is shown in Figure 1.

### 2.2. Patient and public involvement

The study was approved by the Ethics Committee of the First Affiliated Hospital to Changchun University of Chinese Medicine. Informed consent was obtained from all participating patients and their families regarding the use of their data for research purposes. The trial was conducted according to the guidelines stipulated in the Declaration of Helsinki and monitored to follow the guidelines for good clinical practice.

### 2.3. Chronic liver failure diagnosis, cholestatic liver disease diagnosis, and ascites assessment criteria

All patients were hospitalized at the First Affiliated Hospital to Changchun University of Chinese Medicine (No. 1478 Gong-

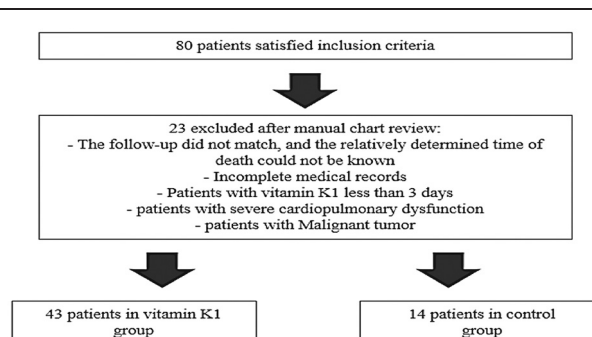


Figure 1. Selection process.

nong Road, Changchun City, Jilin Province, China). The diagnostic criteria for chronic liver failure are based on the China *Guidelines for the Diagnosis and Treatment of Liver Failure*, "Chronic liver failure is based on liver cirrhosis. There is a slow decline in liver function and decompensation, which shows the following: elevated serum TBIL, often < 10× the upper limit of normal (ULN); albumin (ALB) was significantly reduced; significantly decreased platelet count, prothrombin activity < 40% (or INR > 1.5), and excluding other causes; have refractory ascites or portal hypertension; and have hepatic encephalopathy."<sup>[1,2]</sup>

Diagnostic criteria for cholestatic liver disease, according to the 2009 European Society of Liver Diseases (EASL) Cholestatic Liver Disease Treatment Clinical Practice Guidelines Expert Diagnostic Working Group, recommend "ALP > 1.5× the ULN, and gamma-glutamyl transpeptidase (GGT) exceeding 3× the ULN" to diagnose cholestatic liver disease.<sup>[7]</sup>

Ascites evaluation criteria refer to the *Guidelines for Diagnosis and Treatment of Cirrhosis Ascites and Related Complications* classifications, which are as follows: grade 1, depth < 3 cm; grade 2, depth 3 to 10 cm; and grade 3, depth > 10 cm.<sup>[8]</sup>

### 2.4. Data collection and statistical analysis

The endpoint of death was followed up for 48 weeks. The reasons for patients being lost to follow-up include the refusal of the patient's family to cooperate and patients could not be reached via telephone. Demographic information (age and sex) and other medical records and characteristics, such as etiology (alcohol, hepatitis B, hepatitis C, primary biliary cirrhosis (PBC), unknown cause), history of cirrhosis, liver cancer, hepatic encephalopathy, gastrointestinal bleeding, hepatorenal syndrome, cholestatic liver disease, infusion of plasma, vitamin K1 treatment days and doses, initial liver function levels (aspartic acid transaminase [AST], alanine aminotransferase [ALT], ALP, GGT, ALB), initial INR values, and 3 to 5 day INR recorded values, and Child-Turcotte-Pugh score, were collected.

Data were analyzed with IBM SPSS Statistics 22.0.  $P < 0.05$  was considered to be statistically significant. The categorical variables are expressed as numbers or percentages and analyzed by the  $\chi^2$  test. Continuous variables were analyzed with independent sample Mann-Whitney  $U$  test and described as mean  $\pm$  SD. The initial univariate mortality effect analysis was performed using the Cox proportional hazards model followed by multivariate analysis. Survival curves were plotted with the Kaplan-Meier method.

**Table 1****Comparison of baseline characteristics between the vitamin K1 and control groups.**

Variable	Vitamin K1 group (n = 43)	Control group (n = 14)	P value
Age, mean years (SD)*	53.05 ± 10.70	55.21 ± 14.18	0.547
Sex			
Male, no. (%)	33 (76.74%)	11 (78.57%)	1.000
Female, no. (%)	10 (23.26%)	3 (21.43%)	
Cause of liver disease			
Alcohol, no. (%)	7 (16.27%)	5 (35.71%)	0.241
Hepatitis B, no. (%)	31 (72.09%)	6 (42.86%)	0.095
Nucleoside analog therapy† No. (%)	21 (67.74%)	5 (83.33%)	
Hepatitis C, no. (%)	2 (4.65%)	1 (7.14%)	1.000
Primary biliary cirrhosis, no. (%)	1 (2.32%)	0	1.000
Unknown reason, no. (%)	2 (4.65%)	2 (14.29%)	0.25
History of cirrhosis, mean month (range)‡	58.91 (1–240)	36.71 (6–120)	0.479
Ascites, no. (%)	40 (93.02%)	14 (100%)	0.156
None, no. (%)	3 (6.98%)	0	0.568
Small amount, no. (%)	15 (34.88%)	2 (14.28%)	0.26
Medium amount-large amount, no. (%)	25 (58.14%)	12 (85.72%)	0.12
Hepatic encephalopathy			
None, no. (%)	36 (83.72%)	8 (57.14)	0.091
Levels I–II, no. (%)	2 (4.65%)	3 (21.43%)	0.167
Levels III–IV, no. (%)	5 (11.63%)	3 (21.43%)	0.635
Spontaneous bacterial peritonitis, no. (%)	4 (9.30%)	1 (7.14%)	1.0
Hepatorenal syndrome, no. (%)	1 (2.32%)	1 (7.14%)	0.434
Gastrointestinal bleeding, no. (%)	4 (9.30%)	1 (7.14%)	1.0
Cholestatic liver disease, no. (%)	3 (6.98%)	0	0.568
CTP score	12.14 ± 1.28	12.71 ± 1.44	0.271
Class A, no. (%)	0	0	1.0
Class B, no. (%)	1 (2.33%)	0	1.0
Class C, no. (%)	42 (97.67%)	14 (100%)	1.0
Liver function index			
TBIL (μmol/L)–mean (SD)	130.47 ± 129.05	121.21 ± 84.71	0.795
ALB (g/L)–mean (SD)	27.30 ± 4.33	25.36 ± 4.04	0.269
AST (IU/L)–mean (SD)	130.23 ± 134.59	78.71 ± 69.83	0.177
ALT (IU/L)–mean (SD)	90.81 ± 115.10	44.79 ± 34.19	0.191
ALP (IU/L)–mean (SD)	159.30 ± 137.88	136 ± 42.72	0.528
GGT (IU/L)–mean (SD)	92.93 ± 110.07	34.86 ± 36.31	0.003
Plasma, no. (%)	30 (69.77%)	8 (57.14%)	0.586
Plasma dosage, mean ml (range)§	1815.33 (190–7970)	1131.25 (200–3350)	0.16
Vitamin K1, mean days (SD)	16.3 ± 7.85		

ALB = albumin, ALP = alkaline phosphatase, TBIL = total bilirubin.

\* Age at diagnosis of chronic liver failure.

† Patients with hepatitis B who received nucleoside analog therapy (21/31 in the vitamin K1 group, 5/6 in the control group).

‡ History of cirrhosis at the end of hospitalization.

§ Average plasma volume.

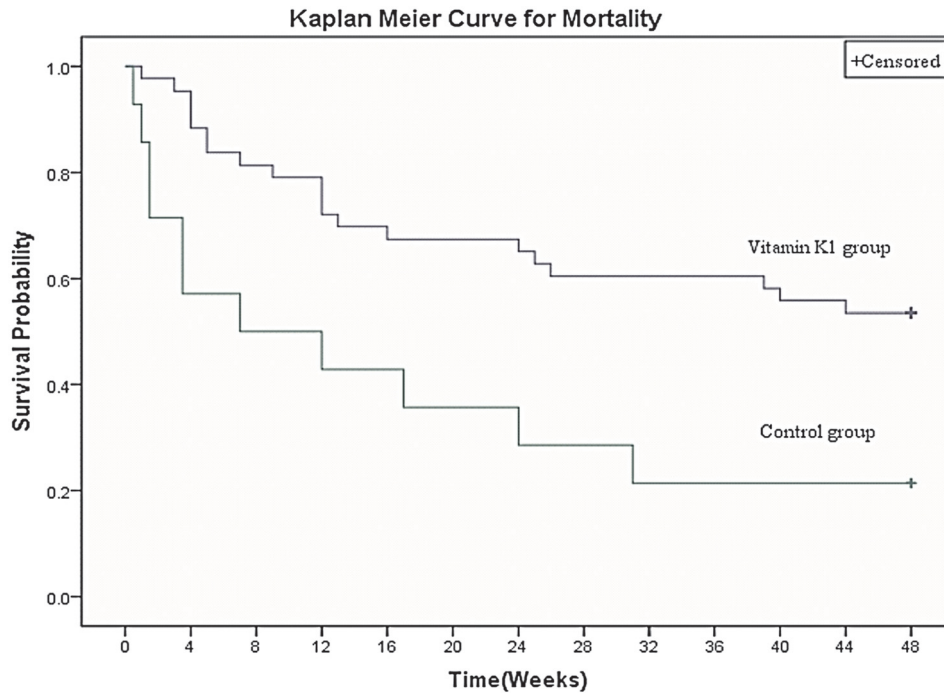
### 3. Results

A total of 57 patients who met the inclusion criteria were analyzed. Patient characteristics are provided in Table 1. The proportion of male patients was higher than that of female patients, with a ratio of 3:1. Three patients in the vitamin K1 group were diagnosed with cholestatic liver disease. Age, sex, etiology, history of cirrhosis, ascites grade, complications, TBIL, ALB, AST, ALT, ALP, and plasma dose were not statistically significant using the chi-square test or independent sample Mann–Whitney U test ( $P > 0.05$ ). Among the variables analyzed, GGT level was significantly different between the 2 groups ( $P = 0.003$ ). Vitamin K1 was used for 3 to 39 days with an average of  $16.3 \pm 7.85$  days.

In the vitamin K1 group, 20 patients (46.51%) died, whereas 11 (78.57%) patients died in the control group. The main cause of death was liver failure and complications. In the Kaplan–Meier analysis, survival time was significantly longer in the vitamin K1

group than in the control group ( $P = 0.006$ ) (Fig. 2). The median time of death in the control group was 7 weeks (95% confidence interval, CI [0.000–22.584]), whereas half of the vitamin K1 group exceeded the mean; hence, the median time to death could not be determined.

The pretreatment INR value of the vitamin K1 group was measured at the first use of vitamin K1, whereas that of the control group was the first test result after admission. The INR values of the two groups were measured 3 to 5 days after treatment, and comparative analysis was performed. Patients with missing INR values before or after treatment were excluded [vitamin K1 group (n = 27) and control group (n = 6)]. The results showed that vitamin K1 reduced the INR levels [ $P < 0.05$  (95% CI 0.000–0.002)], whereas there was no significant change in the INR value in the control group [ $P = 0.26$  (95% CI 0.25–0.27)]. There was no difference found in the INR value between the two groups [ $P = 0.97$  (95% CI 0.91–1.0)] (Table 2). Given that the



**Figure 2.** Mortality in patients who were treated with vitamin K1 compared to the control group. The median time to death was 7 weeks in the control group, whereas in the vitamin K1 group, half of the patients exceeded the average; thus, the median time to death could not be obtained ( $P=0.006$ ).

INR values of some samples greatly varied, to avoid bias, 1 case (INR 3.59–0.96) was excluded from the vitamin K1 group, and 1 case (INR 3.57–6.35) was excluded from the control group.

Univariate analysis using the Cox proportional hazard model showed a significant reduction in the risk of death in the vitamin K1 group (HR 0.37,  $P=0.009$ ). The risk of death was significantly higher in men than in women (HR 2.97,  $P=0.005$ ). Age, ALB, TBil, and ALP were associated with mortality risk (HR 1.044,  $P=0.008$ ; HR 0.854,  $P=0.002$ ; HR 1.004,  $P=0.004$ ; HR 1.004,  $P=0.003$ ). In the multivariate analysis using the Cox proportional hazard model, vitamin K1 reduced the risk of death (HR 0.314,  $P=0.032$ ), and the risk of death in men was significantly higher (HR 3.102,  $P=0.013$ ). Moreover, age, ALB, TBIL, and ALP, and risk of death showed a correlation (HR 1.04,  $P=0.023$ ; HR 0.865,  $P=0.02$ ; HR 1.005,  $P=0.011$ , HR 1.003,  $P=0.032$ ) (Table 3).

#### 4. Discussion

The fields of hepatopathy and coagulopathy have greatly advanced in the past 20 years.<sup>[9–11]</sup> In liver failure, extensive damage to hepatocytes results in insufficient synthesis of

procoagulant and anticoagulant factors, disorders of the fibrinolytic system, insufficient synthesis of thrombopoietin, and immune damage against platelets, thereby aggravating the coagulation dysfunction. Vitamin K is essential for the synthesis of coagulation factors II, VII, IX, and X, and is often associated with vitamin K deficiency in patients with liver failure.<sup>[12]</sup> It is generally believed that vitamin K supplementation can improve the coagulation function of patients with liver failure to some extent. However, the use of vitamin K in the treatment of liver failure has been controversial. China’s 2012 *Guidelines for the Diagnosis and Treatment of Liver Failure* pointed out that “patients with liver failure often have vitamin K deficiency; thus, it is recommended to use vitamin K (5–10 mg)”.<sup>[11]</sup> Moreover, China’s 2018 *Guidelines for the Diagnosis and Treatment of Liver Failure* mentioned that in the case of bleeding, “Vitamin K1 (5–10 mg) can be used for a short time when there is vitamin K1 deficiency”.<sup>[12]</sup> Finally, the AASLD *Acute Hepatic Failure*

**Table 2**  
Comparison of the INR value between the vitamin K1 and control groups.

	Before treatment	After treatment	P value (95% CI)
Vitamin K1 group (n=27)	2.41 ± 0.51	2.18 ± 0.53	0.000 (0.000–0.002)
Control group (n=6)	2.28 ± 0.23	2.16 ± 0.34	0.26 (0.25–0.27)
P value (95% CI)	0.91 (0.81–1.0)	0.97 (0.91–1.0)	

CI=confidence interval, INR=international normalized ratio.

**Table 3**  
Results of the univariate and multivariate analyses of the vitamin K1 group compared to those of the control group.

Variable	Univariate hazard ratio	95% CI	Multivariate hazard ratio	95% CI
Vitamin K1	0.37**	0.176, 0.776	0.314*	0.14, 0.706
Age	1.044**	1.011, 1.078	1.04*	1.006, 1.078
Sex	2.97**	1.382, 6.38	3.102*	1.269, 7.58
ALB	0.854**	0.771, 0.946	0.865*	0.766, 0.977
TBIL	1.004**	1.001, 1.007	1.005*	1.001, 1.008
ALP	1.004**	1.001, 1.006	1.003*	1.000, 1.006

ALB=albumin, ALP=alkaline phosphatase, TBIL=total bilirubin.

\*  $P < 0.05$ .

\*\*  $P < 0.01$ .

*Treatment* in 2011 on coagulopathy treatment suggested that "in a patient with ALF who has vitamin K deficiency, it is recommended to routinely administer vitamin K 5 to 10 mg via subcutaneous injection."<sup>[13]</sup> The 2017 *EASL Management of Acute (Explosive) Hepatic Failure* in Children's ALF states that "children's ALF is a multisystem syndrome, defined as liver-caused coagulopathy manifested as prothrombin time (PT) > 15 or INR > 1.5, and cannot be corrected by vitamin K with clinical HE; or PT > 20 or INR > 2.0 with or without HE."<sup>[15]</sup> In a previous study, during the course of observation of the pharmacokinetic changes of oral and intravenous vitamin K1 in 49 patients with hepatic failure, only 13 patients (27%) had decreased serum K1 levels or elevated PIVKA-2 (des-gamma carboxyprothrombin) concentrations.<sup>[12]</sup> It has also been shown that despite the presence of subclinical vitamin K deficiency, oral vitamin K is not necessary, but it can be corrected by a single intravenous injection of vitamin K. However, the study did not measure indicators of clotting function. In the absence of clinical evidence, the national guidelines in liver failure of when and how to apply vitamin K1 do not have a fully positive opinion. Our study shows that the use of vitamin K1 in patients with chronic liver failure can reduce the risk of death; this is a new finding that has not been reported so far. At the same time, we also found that male sex, age, ALB, TBIL, and ALP are factors that influence the prognosis of chronic liver failure. However, we must clearly understand that there are many factors that affect the death of patients, and further research is needed to confirm the above-mentioned results.

Currently, there are few studies on the effects of vitamin K1 on chronic liver failure. Chronic liver failure is caused by liver dysfunction that started with cirrhosis; thus, we referred to the study of vitamin K1 in the treatment of cirrhosis. Saja investigated the use of vitamin K to correct coagulopathy in cirrhosis and reported hepatitis B carriers, hepatitis B and C, and healthy groups. The control group showed that vitamin K after 72 hours of administration failed to improve PT, activated partial thromboplastin time, thrombin time, fibrinogen, FVII, protein C, total protein, free protein S, and vitamin K deficiency (PIVKA)-II (des-gamma carboxyprothrombin) induced proteins, thereby concluding that vitamin K cannot be used in patients with liver disease.<sup>[13]</sup> Otero believes that vitamin K is not useful for cirrhosis and can be supplemented parenterally only during cholestasis.<sup>[14]</sup> Our study found that vitamin K1 can reduce INR levels, which seems to be inconsistent with studies on cirrhosis. The abovementioned studies did not investigate cholestasis as an influencing factor, which may be the reason why vitamin K1 reduces the INR level in patients with chronic liver failure.

The presence of vitamin K deficiency in cholestasis is common.<sup>[15,16]</sup> Kowdley et al<sup>[17]</sup> showed no correlation between vitamin K1 and prothrombin time in 77 patients with PBC, but decreased vitamin K1 levels were common in PBC patients and were associated with decreased serum levels of vitamins A and E. A study has shown that vitamin K deficiency is prevalent in children with mild to moderate chronic cholestatic liver disease. Vitamin K deficiency is associated with the degree of cholestasis and severity of liver disease in children, but children without cholestasis did not have vitamin K deficiency.<sup>[18]</sup> Mahadevan et al<sup>[19]</sup> suggest that vitamin K should be given immediately in the presence of combined hyperbilirubinemia and failure to obtain coagulation information. Dating back to the earlier literature, a study in 1988 observed vitamin K1 combined with bile acid in the

treatment of hepatocellular cirrhosis, suggesting that vitamin K1 alone is ineffective and effective only in combination.<sup>[20]</sup> Therefore, cholestasis may be the cause of inconsistency in some research conclusions. Our study included only 3 of 57 patients diagnosed with cholestatic liver disease, but vitamin K1 can reduce the risk of death and INR in patients with chronic liver failure; thus, we speculate that the diagnostic criteria for cholestatic liver disease may be overestimated.

Cholestasis in hepatic failure is a severe hepatocytic intra-hepatic cholestasis with mass hepatocyte necrosis as the main cause, and its level was positively correlated with the severity of liver failure.<sup>[21]</sup> Cholestasis is common in liver failure, and the benefit of vitamin K needs to be further verified. It is worth pondering because any treatment that improves the patient's disease state will likely become a way to save the lives of patients with liver failure.

In summary, there are still many problems to be solved in the treatment of liver failure with vitamin K1. Most studies have been able to agree that blind application of vitamin K1 does not improve blood coagulation in patients with liver disease. In this respect, we are basically consistent with the views of Aldrich. In general, it is necessary to treat patients with vitamin K deficiency accompanied with coagulation dysfunction with vitamin K1.<sup>[22]</sup> We agree with the recommendation of Jennifer Strople stating that "Better strategies for vitamin K assessment and guidelines for specific dosing in cholestatic liver disease should be developed."<sup>[15]</sup> However, our study showed that vitamin K1 can reduce the risk of death in patients with chronic liver failure and reduce INR levels, which provides a basis for further research. At the same time, we also believe that vitamin K can be considered when liver failure is accompanied with cholestasis, but the diagnostic criteria for cholestatic liver disease may need to be reassessed. In addition, due to the limitations of medical conditions, not all hospitals are able to perform serologic tests for vitamin K deficiency. In the absence of clear recommendations from relevant studies, clinical pros and cons still need to be weighed to decide whether to apply vitamin K1. For clinicians, the treatment of chronic liver failure with vitamin K1 can reduce mortality. For physician training, it opens up new horizons. For future researchers, cholestasis may be the key to resolving vitamin K1 in the treatment of liver failure.

This study was a single-center retrospective study, and the samples were from the Affiliated Hospital of Changchun University of Traditional Chinese Medicine. Limitations may exist due to geography, culture, race, and sample size (only 14 patients in the control group and 43 patients in the vitamin K1 group). In particular, antiviral therapy and plasma applications may have an impact on endpoint outcomes.

## 5. Conclusions

Vitamin K1 may reduce the risk of death in patients with chronic liver failure. Male sex, age, ALB, TBIL, and ALP are potential risk factors for increased risk of death in these patients. Based on these findings, vitamin k1 can be used in patients with chronic liver failure. Prospective studies are still needed; however, to validate the role of vitamin K1 in the chronic liver failure.

## Acknowledgments

All the authors of this manuscript are very grateful to the various departments of Changchun University of Chinese Medicine for

their support. We would like to thank Editage (www.editage.com) for English language editing.

### Author contributions

Xiong Zhuang is the first author. Zhuang Xiong and Yan Leng obtained funding. Xiong Zhuang, Leng Yan, Liu Yangyang, and Deng Houbo designed the study. Xiong Zhuang and Huo Shaokai collected the data. Chang Tianying, Xu Xiaohao, and Huo Shaokai were involved in data cleaning, mortality follow-up, and verification. Xiong Zhuang, Leng Yan, and Liu Tiejun analyzed the data. Xiong Zhuang drafted the manuscript. Leng Yan and Liu Tiejun contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript. Xiong Zhuang and Leng Yan are the study guarantors.

**Conceptualization:** Zhuang Xiong.

**Data curation:** Shaokai Huo.

**Formal analysis:** Zhuang Xiong, Tianying Chang, Xiaohao Xu, Yan Leng.

**Funding acquisition:** Zhuang Xiong, Yan Leng.

**Investigation:** Zhuang Xiong, Houbo Deng, Yan Leng.

**Methodology:** Zhuang Xiong, Yangyang Liu, Houbo Deng, Yan Leng.

**Writing – original draft:** Zhuang Xiong.

**Writing – review & editing:** Tiejun Liu, Yan Leng.

### References

- [1] Infectious LFaALGCSO, Association DCM, Diseases SL, Hepatology Chinese aALGCSO, Association M, Guidelines for diagnosis and treatment liver failure (2012). *J Pract Hepatol* 2013;16:210–6.
- [2] Infectious LFaALGCSO, Association, D.C.M., Diseases, S.L., Hepatology, Chinese aALGCSO, Association, M., Guidelines for diagnosis and treatment liver failure (2018). *J Clin Hepatol* 2019;35:38–44.
- [3] Lee WM, Larson AM, Stravitz RT. AASLD position paper: the management of acute liver failure: update 2011. *Hepatology* 2011;55:1–22.
- [4] Shearer Martin J. Vitamin K in parenteral nutrition. *Gastroenterology* 2009;137:105–18.
- [5] Wendon J, Cordoba J, et al. European Association for the Study of the LiverEASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure [in Chinese]. *J Hepatol* 2017;66:1047–81.
- [6] Marti-Carvajal Arturo J, Solà Ivan. Vitamin K for upper gastrointestinal bleeding in people with acute or chronic liver diseases. *Cochrane Database Syst Rev* 2015;CD004792.
- [7] European Association for the Study of the LiverEASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009;51:237–67.
- [8] Xu X, Ding H, Li W, et al. Guidelines on the management of ascites and complications in cirrhosis Chinese Society of Hepatology [in Chinese]. *J Clin Hepatol* 2017;33:1847–63.
- [9] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011;365:147–56.
- [10] Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. *Semin Thromb Hemost* 2015;41:468–73.
- [11] Intagliata NM, Argo CK, Stine JG, et al. Concepts and controversies in haemostasis and thrombosis associated with liver disease: Proceedings of the 7th International Coagulation in Liver Disease Conference. *Thromb Haemost* 2018;118:1491–506.
- [12] Pereira SP, Rowbotham D, Fitt S, et al. Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phylloquinone (vitamin K1) in severe acute liver disease. *J Hepatol* 2005;42:365–70.
- [13] Saja MF, Abdo AA, Sanai FM, et al. The coagulopathy of liver disease: does vitamin K help? *Blood Coagul Fibrinolysis* 2013;24:10–7.
- [14] Otero Fernandez MA, Romero-Gomez M, Martinez Delgado C, et al. Usefulness of vitamin K in hepatic cirrhosis [in Spanish]. *Aten Primaria* 1999;24:242–3.
- [15] Stroppe J, Lovell G, Heubi J. Prevalence of subclinical vitamin K deficiency in cholestatic liver disease. *J Pediatr Gastroenterol Nutr* 2009;49:78–84.
- [16] Akimoto T, Hayashi N, Adachi M, et al. Viability and plasma vitamin K levels in the common bile duct-ligated rats. *Exp Anim* 2005;54:155–61.
- [17] Kowdley KV, Emond MJ, Sadowski JA, et al. Plasma vitamin K1 level is decreased in primary biliary cirrhosis. *Am J Gastroenterol* 1997;92:2059–61.
- [18] Mager DR, McGee PL, Furuya KN, et al. Prevalence of vitamin K deficiency in children with mild to moderate chronic liver disease. *J Pediatr Gastroenterol Nutr* 2006;42:71–6.
- [19] Mahadevan SB, Beath SV, McKiernan PJ, et al. The vitamin K debacle and infants with cholestatic liver disease. *Arch Dis Child* 1999;81:278.
- [20] Nambu M, Iijima T. A combination therapy of vitamin K1 and bile acid on hemorrhagic diathesis in patients with decompensated liver cirrhosis. *Gastroenterol Jpn* 1988;23:160–4.
- [21] Qing M. Pathogenesis and management strategies of liver failure-associated cholestasis [in Chinese]. *J Clin Hepatol* 2019;35:258–61.
- [22] Aldrich SM, Regal RE. Routine use of vitamin k in the treatment of cirrhosis-related coagulopathy: is it A-O-K? Maybe not, we say. *P T* 2019;44:131–6.