Effect of vitamin K1 on survival of patients with chronic liver failure
A retrospective cohort study

Zhuang Xiong, MD, PhD, Yangyang Liu, MD, PhD, Tianying Chang, MS, Xiaohao Xu, MS, Shaokai Huo, MS, Houbo Deng, MD, PhD, Tiejun Liu, MS, Yan Leng, MD, PhD

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-squared 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 (HR=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.[1,2] 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
development of acute liver failure, and microcirculation disorders and portal hypertension are common features of chronic liver disease.\(^{[5]}\) 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, VII, IX, and X,\(^{[4]}\) 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,\(^{[1]}\) 2011 AASLD “Acute Hepatic Failure Treatment”, and “EASL clinical practice guidelines on the management of acute (fulminant) liver failure (2017)”\(^{[5]}\) 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.”\(^{[6]}\) 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 K5 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-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 \(\times\) the upper limit of normal (ULN); liver function (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.”\(^{[1,2]}\)

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 \(\times\) the ULN, and gamma-glutamyl transpeptidase (GGT) exceeding 3 \(\times\) the ULN” to diagnose cholestatic liver disease.\(^{[7]}\)

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.\(^{[8]}\)

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, 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 ± 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 (2.3%)                | 0                    | 1.000   |
| Unknown reason, no. (%)                       | 2 (4.65%)               | 2 (14.29%)           | 0.25    |
| History of cirrhosis, mean month (range)†     | 56.91 (1–240)           | 36.71 (6–120)        | 0.479   |
| Ascents, 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 (2.3%)                | 1 (7.14%)            | 0.434   |
| Gastrintestinal 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)                          | 190.23±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               |                      |         |

Vitamin K1 group (n=27) and control group (n=6).

§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±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
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 0.314, \( P = 0.032 \); HR 3.102, \( P = 0.013 \)). 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. 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. 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 (5–10mg)”.[1] Moreover, China’s 2018 Guidelines for the Diagnosis and Treatment of Liver Failure mentioned that in the case of bleeding, “Vitamin K1 (5–10mg) can be used for a short time when there is vitamin K deficiency”.[2] 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 | 2.19±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).

### 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, 6.398 | 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.”[3] 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.”[13] 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 (de-gamma carboxyprothrombin) concentrations.[12] 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 (de-gamma carboxyprothrombin) induced proteins, thereby concluding that vitamin K cannot be used in patients with liver disease.[13] Otero believes that vitamin K is not useful for cirrhosis and can be supplemented parenterally only during cholestasis.[14] 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.[15,16] Kowdley et al.[17] 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.[18] Mahadevan et al.[19] 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.[20] 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 intrahepatic cholestasis with mass hepatocyte necrosis as the main cause, and its level was positively correlated with the severity of liver failure.[21] 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.[22] 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”.[15] 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. Zhuang Xiong and Leng Yan are the study guarantors.

**Conceptualization:** Zhuang Xiong.

**Data curation:** Shaokai Huo.

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

**Funding acquisition:** Zhuang Xiong, Tianying Chang, Xiaohao Xu, 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 Pragtical Guidelines on the management of acute (fulminant) liver failure [in Chinese]. J Hepatol 2017;66:1047–81.

[6] Marti-Carvajal Arturo J, Sola Ivan. Vitamin K for upper gastrointestinal bleeding in patients 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] Lismar T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost 2015;41:468–73.

[11] Intagliata NM, Argu CK, Stine JG, et al. Concepts and controversies in haemostasis and thrombus 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, Fitr S, et al. Pharmacokinetics and efficacy of oral versus intravenous mixed-micellar phylloquinone (vitamin K1) in severe acute liver disease. J Hepatol 2005;42:363–70.

[13] Saja MF, Abd AA, Sanai FM, et al. The coagulopathy of liver disease: does vitamin K help? Blood Coagul Fibrino1ysis 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] Strupple 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] Mahadevan SB, Beath SV, McKiernan PJ, et al. Plasma vitamin K1 level is decreased in primary biliary cirrhosis. J Hepatol 1997;27:2039–61.

[18] Mager DR, McGee PL, Furuuya 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, Litan P, et al. Vitamin K helps? Blood Coagul Fibro1ysis 2004;15:103–7.

[20] Nambu M, Iijima T. A combination therapy of vitamin K1 and bile acid for abdominal pain of cholestasis [in Japanese]. J Hepatobiliary Pancreat Sci 2009;16:272–5.

[21] Mager DR, McGee PL, Furuuya KN, et al. Usefulness of vitamin K in hepatic cirrhosis [in Spanish]. Aten Primaria 1999;24:242–3.

[22] Aldrich SM, Regal RE. Routine use of vitamin K in the treatment of coagulopathy. J Pediatr 1988;113:656–60.