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ORIGINAL ARTICLE

The value of severe vitamin D deficiency in predicting the mortality risk of patients with liver cirrhosis: A meta-analysis

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KEYWORDS
Vitamin D;
Liver cirrhosis;
Mortality risk;
Meta-analysis

Summary
Aim: Vitamin D plays an important role in the pathological process of chronic liver disease (CLD), and the degree of vitamin D deficiency is related to the severity of CLD. The aim of our study was to investigate the association between severe vitamin D deficiency and the risk of all-cause mortality in patients with liver cirrhosis (LC).
Methods: The PubMed, Embase, and Cochrane Library databases were searched systematically for eligible studies from the earliest available date to 15 January 2019. The exposure and outcome of interest was serum vitamin D levels and all-cause mortality, respectively. The pooled risk ratio (RR) values and their 95% confidence intervals (CIs) were calculated through a meta-analysis.
Results: Eight studies published from March 2013 to January 2019 were included, involving 1,339 patients with LC. The meta-analysis showed that a severe serum vitamin D deficiency was associated with an increased risk of mortality in patients with LC (RR = 1.79; 95% CI 1.44—2.22; $P < 0.01$).
Conclusion: Our meta-analysis confirmed the association between severe vitamin D deficiency and mortality risk, suggested serum vitamin D level as a new index to predict the prognosis, and emphasized the importance of vitamin D supplementation in LC patients.

Introduction

An estimated 844 million people worldwide have CLD [1], which induces LC in 633,000 patients annually, with a prevalence ranging from 4.5—9% [2]. Since the exact incidence of decompensated LC is unknown, if decompensation occurs in an estimated 20—25% of patients with LC, this would represent 150,000—200,000 patients per year [3]. Moreover, decompensated LC is the 14th most common global cause of death in adults and results in one million deaths per year worldwide [3]. For these reasons, it is important to find ways to predict the risk of mortality in patients with LC and to provide appropriate treatment. Markers commonly

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used to predict the severity of LC such as Child-Pugh score (CPs) and the Model of End-stage Liver Disease (MELD) Score mainly reflect the degree of liver failure but do not always accurately predict the risk of mortality [4]. Therefore, it is urgently necessary to identify new markers to predict mortality risk.

Vitamin D is initially converted to 25(OH)D3 in the liver. This process occurs mainly through six hepatic vitamin D 25-hydroxylases in the cytochrome P450 family (CYP2C11, CYP2D25, CYP2J3, CYP3A4, CYP27A1, and CYP2R1) and is important for the production of the physiologically active form of vitamin D (1.25(OH)D) [5]. Increasing studies have reported that vitamin D is related to liver diseases, [6,7] and may be useful for the prediction of mortality risk in patients with LC.

A recent meta-analysis suggested that vitamin D deficiency increased susceptibility to severe infections and mortality risk in critically ill patients [8]. Another meta-analysis found that vitamin D supplementation might have a positive effect on all-cause mortality in patients with CLD [9]. However, the result was imprecise because their conclusion was based on a limited number of trials. Those two meta-analyses indicated that vitamin D had a significant influence on the prognosis of patients with CLD and those who were critically ill. As LC is the end stage of CLD and a common cause of critical illness, it is necessary to conduct a meta-analysis of existing studies to determine whether vitamin D deficiency is related to the mortality risk of LC patients.

Materials and methods

Study design

We planned, conducted, and reported this meta-analysis by according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, which are the published standards for meta-analyses of observational studies [10].

Search strategy

A systematic literature search was performed in the PubMed, Embase, and Cochrane Library databases with restriction to the ''Title/Abstract or MeSH/Emtree'' using the following search terms: (vitamin D or 25(OH)D or 25-OH-vitamin D or 25 hydroxyvitamin D or 25 hydroxyl vitamin D or calcitriol) and (liver cirrhosis or liver cirrhoses or liver cirrhotic or chronic liver disease or CLD or liver fibrosis or liver fibroses) and (mortality or survival or death). The search dates were from the earliest available date to 15 January 2019.

Study selection and quality assessment

The included studies were required to meet the following criteria:

- prospective cohort studies of LC patients that contained information necessary to estimate the hazard ratio/risk ratio (HR/RR) values and their 95% CIs of all-cause mortality;
- exposure and outcome of interest was serum vitamin D levels and all-cause mortality, respectively, and;
- studies including more than 30 patients with LC.

The exclusion criteria were:

- studies in which the participants were younger than 18 years of age, sample size of fewer than 30 patients, and with participants with liver failure or other severe diseases with life expectancies of less than one year;
- studies with inadequate data or using animal models; and;
- case-only studies, conference articles, letters, or reviews.

For our meta-analysis, two independent investigators screened the article titles and abstracts for eligibility. In the case of disagreement, a third author provided a final opinion. The methodological quality of the studies was assessed using the nine-star Newcastle-Ottawa Scale (NOS) for cohort studies. Studies with six or more stars were considered to be of high quality [11].

Definition of severe vitamin D deficiency

25(OH)D is the most stable and plentiful vitamin D metabolite in human serum, with a half-life of about 3 weeks, making it the most suitable indicator of vitamin D status. [12] A concentration of 30—100 ng/mL was defined as sufficient, while levels < 20 ng/mL were defined as deficient [13,14,15]. In the present study, we defined severe vitamin D deficiency as a concentration of less than 10 ng/mL.

Statistical methods

Stata/SE version 12.0 (Stata Corporation, USA) was used to perform the meta-analysis. We calculated the RR values and their 95%CIs for each study, transformed them into ln(RR) /ln(LCI)/ ln(UCI), and pooled them using Stata/SE. If studies presented univariate and multivariate HR values of mortality risk, we used the multivariate HR value as the RR value. In the case of studies presenting only univariate HR values for mortality risk, we used it as the RR value. If the included studies did not provide a HR or RR value, we manually calculated the RR value using the available data.

Heterogeneity was estimated using the chi-squared test and the I^2 method. [16,17] Heterogeneity was defined as a Chi^2 *P*-value of less than 0.10 or I^2 value of more than 50%, in these cases, the random-effect model was used to pool the data [18]. If there was no obvious heterogeneity among the included studies, the fixed-effect model was used. Sensitivity analysis was performed by omitting each study in turn to test the changes in pooled RR values. Meta-funnel plot and meta-trim plot in Stata/SE were used to estimate the risk of publication bias.

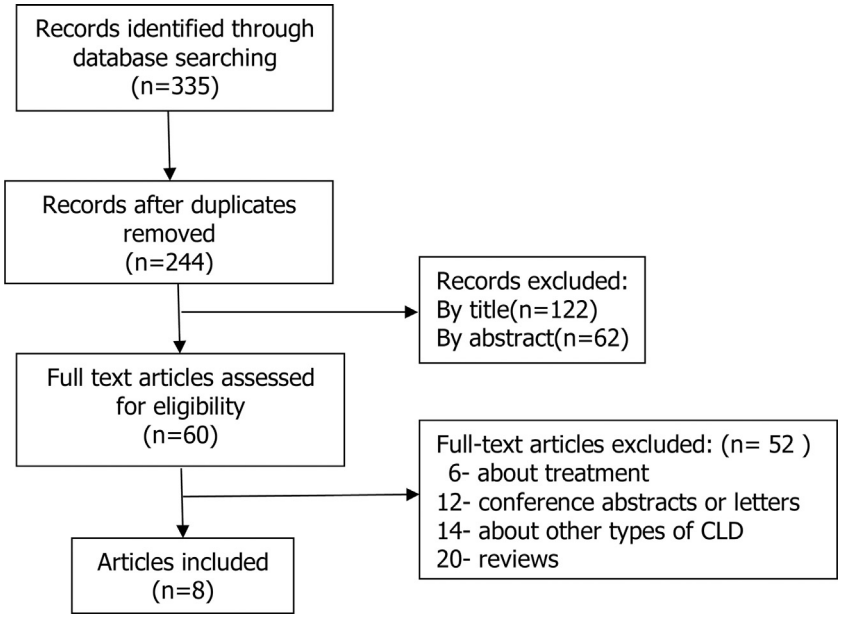

Figure 1 Flow chart of selection of included studies.

Results

Literature search and study characteristics

A total of 335 articles (PubMed = 45, Embase = 264, Cochrane Library = 26) were screened, 327 of which were excluded for duplicate articles ($n = 91$), irrelevancy (by title = 122, by abstract = 62), treatment ($n = 6$), conference abstracts or letters ($n = 12$), other type of CLD ($n = 14$), and reviews ($n = 20$). A total of eight studies met the inclusion criteria and were finally included in the meta-analysis. Fig. 1 shows a flowchart of the selection of the included studies. All studies included in this meta-analysis were prospective cohort studies [19—25]. We assessed the quality of included studies based on NOS criteria. Five and three studies were of high and moderate quality, respectively. Six studies provided HR values directly (by univariate or multivariate analysis) and HR values were manually calculated in the remaining studies. The included studies contained a total of 1339 patients and were published from March 2013 to January 2019.

As shown in Table 1, the included studies had the following characteristics:

- the included studies were all performed in developed countries in Europe, so there were few differences in geographical characteristics and economic levels;
- the main etiology of LC was alcoholism, except for hepatitis C in the study by Buonomo et al., and;
- there were no significant differences in age and gender composition among the included studies.

The average follow-up time ranged from 147—419 days, the average MELD Score ranged from 8.2—26.0, the proportion of Child-Pugh Score of B or C (CPs B + C%) ranged from 22.3—79.0% (CPs C%), and the mean serum 25(OH)D concentration ranged from 7.0—16.0 ng/mL after excluding studies with incomplete data.

Effect of severe vitamin D deficiency on all-cause mortality risk

As there was no obvious heterogeneity among the eight included studies ($I2 = 29.4\%$; $P = 0.184$), the fixed-effect model was used to pool data. The pooled RR value was 1.79 (95% CI 1.44—2.22; $P < 0.01$). The pooled CI did not include 1.00, indicating the credibility of the pooled RR value. Subgroup analysis was also performed according to serum vitamin D levels Fig. 2. Studies with serum vitamin D levels of < 6 and < 10 ng/mL (including the study with serum vitamin D level < 8.8 ng/mL) were classified as subgroups 1 and 2 respectively. Subgroup analysis revealed that the pooled RR value of subgroup 1 was higher than that subgroup 2 (1.86 vs. 1.75), indicating that the more serious the vitamin D deficiency, the higher the risk of mortality.

The potential risk of publication bias was estimated by inspection of meta-funnel plot and Egger's test. The meta-funnel plot showed no asymmetry between the lower left and lower right corners (Fig. 3). In addition, the p-value for Egger's test was less than 0.05 ($P > |t| = 0.026$). Therefore, there was some publication bias in the meta-analysis and the meta-trim method was used to assess the robustness of our results. After adding three results by the meta-trim method, the pooled RR value was 1.62 (95%CI 1.32—1.99; $P < 0.01$). The adjusted RR value was close to the pooled RR value (1.62 vs. 1.79), the adjusted P-value was less than 0.01, and the 95% CI did not include 1.00, indicating that our results were robust (Fig. 4).

Discussion

Our meta-analysis showed that severe vitamin D deficiency was associated with increased all-cause mortality risk in patients with LC. Although only eight eligible studies were included and there was publication bias, our results were still robust because there was no obvious heterogeneity

Table 1 Characteristics of included studies.

Author and year	Country	No. of patients	Age (y)	Gender (M/F)	Died	Mean serum 25(OH)D concentration (ng/ml)	Definition of severe vitamin D deficiency (ng/ml)	HR (Univariate/ Multivariate) or RR value of mortality risk	Follow-up time (day)	MELD score	Correlation[e]	CPs B + C %[g]	Correlation[i]	The main etiology of LC	Covariates[j]
Fabian Finkelmeier1 (2015)	Germany	251	57 (25—84)	171/80	85 (33.9%)	8.9 ± 7.1	< 6	1.723/1.703	411 (1—1382)	15.0 (6.0—40.0)	$r = -0.227$ $P < 0.001$	79.7%	r: NA $P < 0.001$	Alcoholic (61%) Hepatitis C (29.5%) Hepatitis B (13.5%) Cryptogenic (9.2%)	age, gender, HCC, serum sCD163 levels, infection, CPs, MELD score
Fabian Finkelmeier2[a] (2015)							< 10	NA/1.424							
Rodolphe Anty (2014)	France	88	58.5 (51.3—67)	58/30	30 (34.1%)	8.8(5.3—14.1)[b]	< 10	0.994(RR)[c]	212 (66—344)	12.3	no correlation[f]	77.0%	$r = -0.28$ $P = 0.009$	Alcoholic (55.8%) Hepatitis C (10%) Alcoholic and Hepatitis C (9%)	NA
Rafael Paternostro (2016)	Austria	199	57 (38—69)	147/52	42 (21.1%)	12.0(4.0—31.3)[b]	< 10	NA/1.86	419 (22—1048)	12.0 (6.4—24.0)	$r = -0.223$ $P = 0.002$	71.4%	$r = -0.235$ $P < 0.001$	NA	age, HCC, CSPH, CPs
Caroline S Stokes (2014)	Germany	65	58 (19—76)	43/22	31 (47.7%)	8.2(4.0—95.8)[b]	< 6	NA/2.11[c]	730[d]	15.3 (9.0-21.7)	NA	81.5%	NA	Alcoholic (66.2%) Cryptogenic (12.3%) Viral (10.8%)	age, gender, MELD score, etiology
Ulrich Mayr (2018)	Germany	62	58 (52—69)	36/26	44 (71.0%)	7.0(4.8—10.0)[b]	< 10	2.20(RR)[c]	180[d]	26.0 (19.0—32.0)	$r = -0.281$ $P = 0.027$	79.0%[h]	$r = -0.263$ $P = 0.039$	Alcoholic (61%) Cryptogenic (19%) Viral (15%)	NA
Eric Trépo (2013)	Belgium	254	NA	NA	32 (12.6%)	NA	< 10	5.95/4.33	147 (NA)	NA	NA	NA	NA	Alcoholic (100%)	age, gender, MELD score, BMI
Csilla P Bankuti (2012)	Austria	75	57.7 ± 10.6	51/24	24 (32.0%)	16.0 ± 9.2	< 8.8	NA/2.73	1260[d]	12.9 (8.7—17.2)	$r = -0.33$ $P = 0.006$	56.0%	$r = -0.21$ $P = 0.095$	Alcoholic (61%) Hepatitis C (19%) NAFLD (13%)	age, gender, MELD score or CPs[k]
Antonio R Buonomo (2019)	Italy	345	68 (61—74)	268/77	54 (15.7%)	15.0(8.0—24.0)[b]	< 10	2.19/4.33	270 (180—480)	8.2 (5.7—11.0)[c]	NA	22.3%	NA	Hepatitis C (97.1%)	HCC, MELD score, CPs, AFP

NA: not applicable; M: male; F: female; 25-OH(D): 25-hydroxylvitamin D; CPs: Child-Pugh Score.

[a] The same study as the first.
[b] Median (interquartile range).
[c] Manually calculated.
[d] The longest follow-up time.
[e] Correlation between serum 25(OH)D concentration and MELD Score.
[f] The concrete values are not applicable.
[g] The proportion of Child-Pugh Score B or C.
[h] The proportion of Child-Pugh Score C.
[i] Correlation between serum 25(OH)D concentration and CPs B + C%.
[j] Covariates used in multivariate analysis for predicting mortality risk.
[k] When the covariates were äge, gender, CPs,, the HR value was 3.06 ($P = 0.06$).

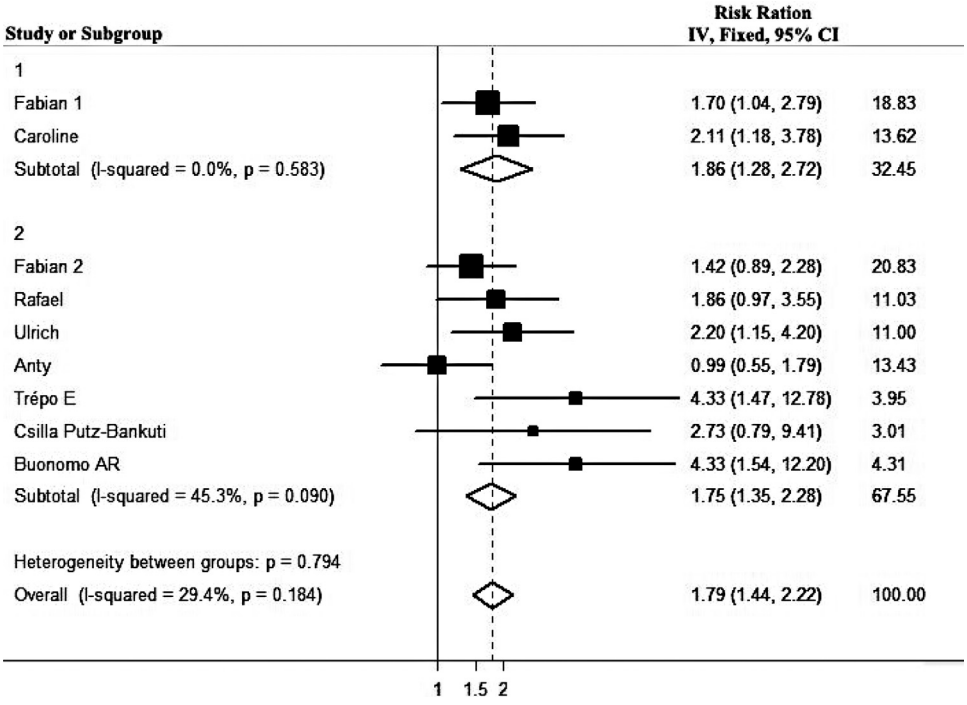

Figure 2 Forest plot and pooled relative risk (RR).

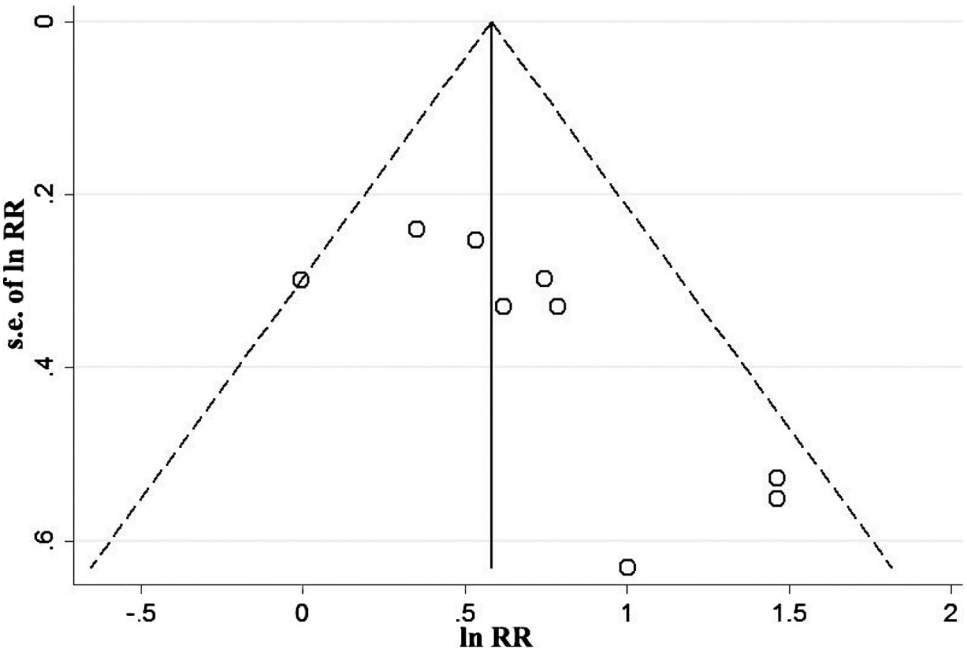

Figure 3 Meta-funnel plot.

(I^2 = 29.4%; P = 0.184) and the meta-trim method showed our results to be reliable. In addition, six of the included studies used multivariable-adjusted HR values rather than RR values, making them more accurate in predicting the actual mortality risk of patients with LC, which further strengthened the robustness of our results.

In our meta-analysis, four studies reported inverse correlations between average MELD Score and mean serum 25(OH)D concentration. Five studies also observed inverse correlations between average CPs and mean serum 25(OH)D concentration. Since average MELD score and CPs are important indexes that reflect disease severity in LC patients, their correlations with mean serum 25(OH)D concentration enhances the fact that severe vitamin D deficiency is associated with the severity of LC. Five studies used MELD score and four studies used CPs as a covariate in multivariate analysis, which showed that severe vitamin D deficiency was independent of MELD score and CPS to some degree. One

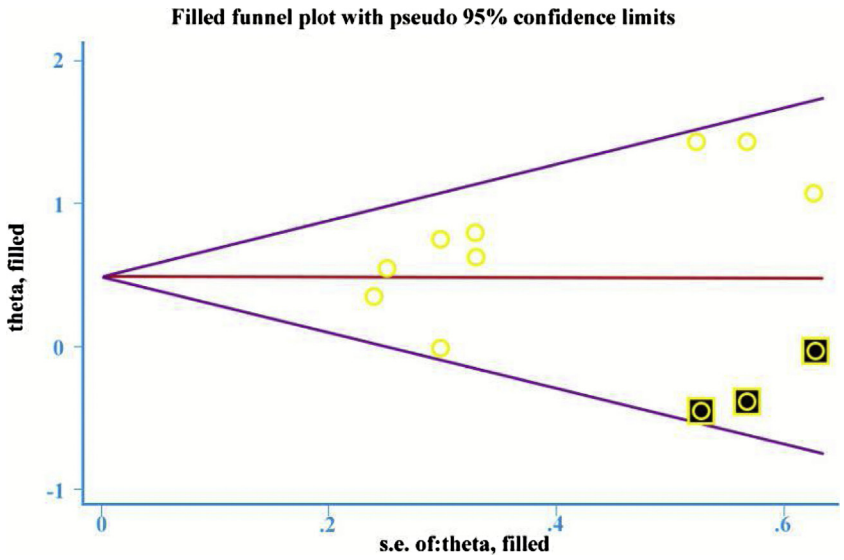

Figure 4 Meta-trim plot.

Table 2 Evidence for vitamin D deficiency as a risk factor of infection.

Author	No. of Patients	Evidence by multivariate analysis	Explanation
Rodolphe Anty	88	vitamin D < 10 ng/mL, OR = 5.44, 95% CI: (1.35—21.97), $P = 0.017$	OR > 1 means that vitamin D deficiency is a risk factor for infection
Buonomo AR	291	vitamin D < 20 ng/mL, OR = 3.09, 95% CI: (1.35—7.07), $P = 0.017$	
Haidi KR	87	vitamin D level (ng/mL), EXP(B) = 0.93 95% CI: (0.854—0.959), $P < 0.01$	Exp(b) < 1 means that vitamin D level is negatively correlated with infection

study using infection as a covariate in multivariate analysis found severe vitamin D deficiency to be an independent predictor, but the result was not definitive because more studies were required for confirmation.

Infection is a common complication and cause of death in LC. A previous meta-analysis showed four-fold increased mortality due to infection in LC patients [26]. Recently, three clinical studies found that vitamin D deficiency was an independent predictor for infection of LC patients (Table 2) [20,27,28] and a study conducted by Buonomo et al found that a serum-ascites vitamin D gradient was associated with spontaneous bacterial peritonitis [29]. Additionally, from a molecular biology perspective, vitamin D can be synthesized by immune cells in response to infection and has immune regulatory functions for the induction of antimicrobial peptides and Th2 cytokines, suppression of innate immune response, and stimulation of T-regulatory T cells [30]. Thus, vitamin D deficiency affects the normal function of the immune system and increases mortality via increased risk of infection. However, by meta-analysis, vitamin D deficiency was found to be associated with mortality risk in many diseases other than LC such as dialysis, [31] chronic kidney disease, [32] cardiovascular disease, [33] and critical illness, [34] suggesting that vitamin D deficiency may have more complex pathomechanisms.

However, whether vitamin D deficiency is the cause or consequence in the pathological process of LC is uncertain. On the one hand, as very few foods naturally contain vitamin D, the major cause of vitamin D deficiency is due to inadequate exposure to sunlight, dysfunction of vitamin D activation in liver and kidney, and decreased levels of plasma binding proteins. Compared to unaffected individuals, patients with LC have less exposure to sunlight, poorer nutrition supply, and worse liver function. Therefore, vitamin D deficiency may be a consequence of the progression of LC.

On the other hand, vitamin D deficiency can lead to a worse prognosis of LC for the following reasons:

- as vitamin D can have an⅓anti-fibrosis⅓effect via the vitamin D receptor-Sma-Mad protein-hepatic stellate cell (VDR-SMAD-HSC signaling loop, vitamin D deficiency aggravate the development of fibrosis [35];
- vitamin D can also⅓reduce the production⅓of⅓body smooth⅓muscle actin⅓and collagen, thus inhibiting the progression of⅓LC⅓induced⅓by thioacetamide [36];
- as mentioned above, vitamin D deficiency also has an important effect on the normal function of the immune system.

For these reasons, vitamin D deficiency is likely to be both a cause and consequence in the pathological process of LC and plays multiple roles in the prognosis.

The association between severe vitamin D deficiency and the risk of mortality suggests that serum 25(OH)D level can be used as a new marker to identify LC patients at high risk of mortality and that vitamin D supplementation may be helpful for reducing the risk of mortality. Thus, it is essential to determine whether vitamin D supplementation can improve the prognosis of patients with LC. However, there are limited studies on the relationship between vitamin D supplementation and prognosis and which type of vitamin D supplementation is better in LC patients.

A randomized controlled trial conducted by Stefan Pilz et al suggested that vitamin D supplementation was unable to remediate established fibrosis [37]. Another prospective cohort study on the prognosis of patients with decompensated LC found that vitamin D supplementation was significantly ($P < 0.05$; adjusted HR = 0.48) associated with the survival of patients over six months [38].

In addition, a meta-analysis of ordinary patients found that vitamin D supplementation was effective in preventing all-cause mortality in long-term treatment but was not significantly effective in a treatment duration of fewer than three years, [39] indicating that a longer duration of supplementation was important for reducing mortality risk. For these reasons, vitamin D supplementation is essential for LC patients even though it cannot remedy established fibrosis. The 2018 EASL Clinical Practice Guidelines also recommend oral vitamin D supplementation in LC patients with vitamin D level < 20 ng/mL to reach serum levels > 30 ng/mL (evidence quality: Grade II-1, B1) [40].

The findings of our meta-analysis have several limitations. First, the studies included were all conducted in European countries; thus, the results might not represent the reality of the world, especially in developing countries. Additional prospective cohort studies with larger numbers of participants need to be conducted in other populations to minimize potential disease-effect nonconformity among countries. Second, we used the RR instead of HR value in two of the included studies, which might reduce the robustness of our results. Finally, despite the fact that the meta-trim method indicated that our results were robust, the ability to detect publication bias in the meta-trim method might decrease when only eight studies were included. Hence, we are unable to exclude all possibility of publication bias in the meta-analysis.

To summarize, our meta-analysis showed that severe vitamin D deficiency was associated with a higher risk of mortality in patients with LC. Because of the limited number of studies, more prospective cohort studies with larger numbers of participants are needed to further assess the association between severe vitamin D deficiency and mortality risk in LC patients. Our results also support the recommendation for vitamin D supplementation in LC patients and highlight the urgent need for further randomized controlled trials to evaluate the impact of vitamin D supplementation on the prognosis of patients with LC.

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Author contributions

All authors contributed to this work. Fuwei Yang and Huina Ren designed the study and analyzed the data. Fuwei Yang, Huina Ren, Yue Gao, and Yali Zhu performed the research and extracted the data. Fuwei Yang prepared Figures and Tables and wrote the paper.

Disclosure of interest

The authors declare that they have no competing interest.

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