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Incidence and prevalence of venous thromboembolism in chronic liver disease: A systematic review and meta-analysis

Mohsan Subhani [a,b,*], Abhishek Sheth [a,b], Jamal Ahmed [c], Pramudi Wijayasiri [a,b], Syed A. Gardezi [c], Doyo Enki [d], Joanne R. Morling [a,b,e], Guruprasad P. Aithal [a,b], Stephen D. Ryder [a,b], Aloysious D. Aravinthan [a,b]

[a] Nottingham Digestive Diseases Centre (NDDC), Translational Medical Sciences, School of Medicine, University of Nottingham, NG7 2UH, UK
[b] NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, NG7 2UH, UK
[c] Royal Gwent Unit, Royal Gwent Hospital, Newport, NP20 2UB, UK
[d] School of Medicine, University of Nottingham, UK
[e] Division of Epidemiology and Public Health, University of Nottingham, Nottingham, NG5 1PB, UK

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ABSTRACT

Background and aims: Historically, bleeding was thought to be a frequent and fatal complication of liver disease. However, thrombosis due to coagulation disorders in cirrhosis remains a real risk. We aim to systematically analyse published articles to evaluate epidemiology of venous thromboembolism (VTE) in chronic liver disease (CLD).

Method: Electronic search was conducted on Ovid Medline, EMBASE and Scopus from inception to November 2021 to identify studies presenting epidemiology VTE (deep vein thrombosis and pulmonary embolism) in CLD in inpatients and/or community settings. Random-effects meta-analysis was performed to determine pooled per-year cumulative incidence, incidence rate and prevalence. Heterogeneity was measured by I^2 test, and, potential sources of heterogeneity by meta-regression and sensitivity analysis. PROSPERO registration-CRD42021239117.

Results: Twenty-nine studies comprising 19,157,018 participants were included, of which 15,2049 (0.79%) had VTE. None of the included studies were done in the community. In hospitalised patients with CLD: pooled cumulative incidence of VTE was 1.07% (95% CI 0.80,1.38) per-year, incidence rate was 157.15 (95% CI 14.74,445.29) per 10,000 person-years, and period prevalence was 1.10% (95% CI 0.85,1.38) per year. There was significant heterogeneity and publication bias. Pooled relative risk (RR) of studies reporting incidence rate was 2.11 (95% CI 1.35,3.31). CLD patients ($n = 1644$), who did not receive pharmacological prophylaxis were at 2.78 times (95% CI 1.11, 6.98) increased risk of VTE compared to those receiving prophylaxis.

Conclusion: Hospitalised patients with CLD may be at an increased risk of VTE. For every 1000 hospitalised patients with CLD ten have new, and eleven have pre-existing diagnoses of VTE per-year.

1. Introduction

Venous thromboembolism (VTE) in chronic liver disease (CLD) is an increasingly encountered complication [1]. Although, traditionally, bleeding was thought to be a frequent and fatal complication of CLD, evidence now supports that an auto-anticoagulatory state in CLD can predispose to thrombosis [2,3]. Liver plays a pivotal role in the regulation of coagulation pathways by producing both pro-coagulant and anti-coagulant factors [4]. Significant impairment in liver synthetic function causes a state of dynamic disequilibrium in haemostasis, which may increase the risk of both bleeding and thromboembolic events [5]. CLD-associated coagulopathy is due to complex alterations in liver and vascular endothelial haemostatic factors, such as reduced protein C, protein S and antithrombin, and increased Von Willebrand factor and factor VIII [6]. These pathophysiological haemostatic

* Corresponding author at: Queens Medical Centre, Derby Road, Nottingham NG72UH, UK.
E-mail addresses: mohsan.subhani@nottingham.ac.uk (M. Subhani), abhishek.sheth@nottingham.ac.uk (A. Sheth), jamal.ahmed@wales.nhs.uk (J. Ahmed), pramudi.wijayasiri@nottingham.ac.uk (P. Wijayasiri), syed.gardezi@wales.nhs.uk (S.A. Gardezi), doyo.enki@nottingham.ac.uk (D. Enki), joanne.morling@nottingham.ac.uk (J.R. Morling), guru.aithal@nottingham.ac.uk (G.P. Aithal), stephen.ryder@nuh.nhs.uk (S.D. Ryder), Aloysious.aravinthan@nottingham.ac.uk (A.D. Aravinthan).

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Nomenclature

CLD	Chronic liver disease
DVT	Deep vein thrombosis
HCC	Hepatocellular carcinoma
INR	International normalised ratio
NAFLD	Non-alcoholic fatty liver disease
PE	Pulmonary embolism
RR	Relative risk
VTE	Venous thromboembolism

changes in turn can promote a procoagulant state translating to an increased risk of thrombosis [7,8].

According to 2017 Global Burden of Disease study, CLD is attributed to two million deaths per year worldwide, over half of these deaths are due to complications of cirrhosis [9,10]. Chronic changes in liver architecture can eventually lead to significant hepatic dysfunction and result in fatal complications including coagulation disorders, hepatorenal syndrome, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatocellular carcinoma [11]. Management of these complications often requires recurrent hospital admissions. Hospitalisation, burden of comorbidities, hepatic synthetic dysfunction and periods of immobility significantly increase the risk of VTE; deep vein thrombosis (DVT) and pulmonary embolism (PE) [12].

Liver focused interventions in hospital have helped to reduce in-hospital mortality in patients with CLD [13], whereas, the in-hospital mortality in CLD after a thrombotic event remains a significant concern [14,15]. A Danish nationwide cohort study reported a 7% (95% CI 5, 10%) 30-day mortality in patients with DVT and cirrhosis compared to 3% (95% CI 2,3%) in patients with DVT but without cirrhosis. The 30-day mortality was 35% (95% CI 29, 42%) in patients with PE and cirrhosis compared to 16% (95% CI 14–19%) in patients with PE but without cirrhosis [15]. Hospitalised patients with cirrhosis who develop VTE during hospital stay are at twice increased risk (OR 2.16, 95% CI 1.96, 2.38) of in-hospital death compared to those without VTE [14].

Incidence rate of VTE (DVT and PE) in all hospitalised patients has been reported to be as high as 960 per 10,000 person years, whereas the incidence rate is at least 100 times lower in community residents (7.1 per 10,000 person years) [16]. In hospitalised patients 4 to 12% have VTE events, and VTE contributes to 7 to 10% of all in-hospital deaths [17,18]. There is significant heterogeneity in the reported incidence of VTE in CLD with some researchers reporting a lower risk and others a higher risk. Reported incidences of VTE in hospitalised patients with cirrhosis varies between 0.33 and 6.32% [19,20]. Results from previous systematic reviews have been conflicting. Qi et al.; (2014) reported a cumulative incidence of 1.0% [20], while, Ambrosino et al.; (2017) reported a 3.7% of VTE (DVT and PE) in hospitalised patients with CLD [2]. Moreover, since the publication of the above systematic reviews [2,20], there has been substantial new data examining epidemiology of VTE in CLD. Nine new studies [21–29] that were not included in the previous systematic reviews, comprising over seven million participants and sixty thousand VTE events (DVT and/or PE) have been published. We aim to systematically analyse published articles to evaluate the epidemiology of VTE in patients with CLD, and to compare relative risk of VTE in patients with CLD to those without CLD.

2. Methods

Joanna Briggs Institute's methodological guidelines for systematic reviews of observational studies reporting prevalence and incidence [30] and Meta-analyse Of Observational Studies in Epidemiology (MOOSE) guidelines were followed [31]. Protocol was registered on Prospero (CRD42021239117).

2.1. Search strategy

We searched Ovid Medline, EMBASE and Scopus from databases inception to 2nd November 2021. Search for grey literature was conducted using Open Grey, Ethos, Google scholar, and clinical.trials.gov. Reference list of included articles was manually searched. Condition, Context, population (CoCoPO) model-based search strategy was developed [30,32]. The search strategy was developed in consultation with expert an expert librarian.

Different combinations of following search terms were used; “Chronic liver disease”, or “Cirrhosis” or “Cirrhotic”, or “Cirrhosis” or “end stage liver disease”, or “CLD” or “advanced liver fibrosis” or “decompensated liver disease” Or (CLD and liver), “liver cirrhosis” or “Cirrho$” or “CLD adj2 VTE”, or “Cirrhosis adj3 VTE”, or “CLD adj3 venous, “(‘liver’ or ‘hepatic’)”, or thromboembolism”, or “Cirrhosis adj3 venous thromboembolism”, AND “Venous thromboembolism”, or “deep vein thrombosis”, or “deep venous thrombosis”, or “pulmonary embolism”, or “VTE” or “DVT”, or “PE” or, “venous thrombosis”, or “thrombotic disease”, or “thromboembolic disease”, AND, “Inpatient”, or “hospitalised”, or “Hospital”, or “Hospitali$ed”, or “secondary care”, or “in patient”, OR, “outpatient”, or “out-patient”, or “community”, or “out of hospital”, or “primary care”, AND (“incidence” or “prevalence” or “epidemiology” or “risk” or “predictor” or “predictive”).

In cases of missing data, abstract only publication and data enquiry, the corresponding author of the study was contacted.

2.2. Eligibility

2.2.1. Inclusion criteria

Studies reporting incidence and/or prevalence of VTE (DVT and PE), in adult patients with CLD including cirrhosis in hospital or community setting were included. CLD was diagnosed based on clinical presentation, laboratory tests, radiological imaging, or liver biopsy, and VTE was diagnosed on radiological imaging.

2.2.2. Exclusion criteria

- Systematic reviews, literature reviews, and editorials
- Studies reporting incidence of VTE post liver transplant, liver resection, and in patients with hepatocellular carcinoma (HCC), or after treatment for HCC.
- Studies which had insufficient data to determine pooled incidence or prevalence

2.3. Outcomes

2.3.1. Primary outcome

Primary outcome was to describe weighted average (pooled) of cumulative incidence (per year), incidence rate (person-years), and period prevalence (per year) of VTE (combined DVT and PE) in patients with CLD.

2.3.2. Secondary outcomes

Secondary outcomes were:

- DVT and PE analysis separately
- Case versus control analysis for studies included control cohort without CLD
- Case versus control analysis for VTE prophylaxis versus no VTE prophylaxis

Based on descriptions in the included studies the following definitions were adopted for the current systematic review.

2.3.3. Cumulative incidence (per year)

Number of new cases of VTE in hospitalised patients with CLD over 1 year per total number of CLD patients hospitalised in that year.

2.3.4. Incidence rate (person-years)

New cases of VTE in hospitalised patients with CLD per 10,000 person years.

2.3.5. Period prevalence (per year)

Number of cases who had pre-existing diagnosis of VTE in hospitalised patients with CLD in 1 year per total number of CLD patients hospitalised in that year.

2.4. Screening and data extraction

Two reviewers (MS and SAG) independently screened the titles and abstracts for eligibility, removed duplicate entries, and recorded reviewers' decisions using Rayyan-QRCI systematic review software, Endnote (version-X9) and Microsoft Excel. Third reviewer (PW) oversaw the process and resolved any conflicts in discussion with senior author (ADA). A three-stage data extraction approach was adopted. First, the review team met at the start to finalise the data extraction proforma and conducted a pilot data extraction to ensure consistency of data extraction and resolved any queries. Second, four reviewers in two pairs (SAG and JA, MS and AS) independently extracted data from the included studies, fifth reviewer (PW) cross checked extracted data for any inconsistencies or errors. Third, the final data extraction was independently reviewed by the senior author (ADA) to resolve any conflicts.

2.5. Quality assessment

Quality and risk of bias assessment for included studies was carried out using Critical Appraisal Skills Programme (CASP) tool [33].

2.6. Data synthesis and analysis

Statistical analysis was carried out using RStudio version 4.0.2 (2020-06-22).

Descriptive statistics were calculated to determine number of events (VTE) and sample size. Due to the presence of significant heterogeneity among included studies a random effects meta-analysis was conducted. Where heterogeneity was non-significant a fixed effects meta-analysis was conducted. Point estimates (per year), incidence rate (person-years) and period prevalence (per year) with 95% confidence interval (CI) from individual studies were pooled using DerSimonian-Laird random effects methods [34], with variations in raw proportion dealt with using the Freeman–Tukey double arcsine transformation [35]. CI for variance between studies were calculated using Jackson method for confidence interval of tau [2] and tau [36]. Whereas Clopper-Pearson method was used to determine confidence interval for individual studies [37]. Pooled cumulative incidence and period prevalence were reported per 100 patients per year with 95% CI. Pooled incidence rate was reported as per 10,000 person years with 95% CI. Heterogeneity between studies was calculated using 'I^2'. An $I^2 > 50\%$ indicated significant heterogeneity. Differences between subgroups was assessed using Cochran's Q (chi-square). Forest plots were used for graphical display of estimated study results and funnel plots for publication bias. Significance of publication bias was confirmed using contour enhanced funnel plot and by Egger's test [38,39].

Where data was not suitable for meta-analysis, a narrative description was performed. Data from included studies were analysed for the intended primary outcome. Where available, the main data were analysed per protocol secondary outcomes.

In priori subgroup analysis was done for study region, sample size, study quality, and sex. Data was insufficient for separate analysis for comorbidity (history of recent surgery, diabetes, cardiovascular diseases), severity of CLD, and aetiology of CLD.

Given the significant variability in pooled effect size and heterogeneity between studies a sensitivity analysis was undertaken by restricting the meta-analysis to (a) year of publication (before 2010 or after 2010), (b) sample size (>10,000 or <10,000), (c) publication type (abstract only or full text), and (d) information on associated malignancy or missing. The cut-off for year of publication was decided based the fact that most literature discussing the safety and efficacy of VTE prophylaxis in CLD were published after 2010 [21,40,41]. The studentized residual tests and leave-one-out analysis were done to determine the impact of outlier and individual studies on effect size [42]. Baujat [43] and r diagnostic tests for influential studies [42] plot were used to graphically display the results. To further ascertain source of heterogeneity a meta-regression analysis was conducted to evaluate the impact of baseline covariates (age, sex, quality of included studies, sample size, publication type, study region) on heterogeneity. Covariates which were significant in univariable analysis were included in multivariable meta-regression.

3. Results

After screening of titles and abstracts, 84 studies were selected for further search, 29 studies [3,12,14,17,21–29,44–59] reporting incidence or prevalence of VTE in CLD were included (Fig. 1). All included studies were of observational design; 18 were conducted in the USA, four in Europe and seven in Asia. None of included the studies were done in the community. Of the included studies, 16 reported incidence, 11 prevalence, and two reported both. In 20 studies included participants had a diagnosis of cirrhosis, and in nine studies CLD, Enger et al. [57] included both. Characteristics of included studies are summarised in Table 1.

3.1. Participants

A total of 19,157,018 participants were included; of which 152,049 (0.79%) had VTE. Mean age of participants was 56.1 years (SD ± 4.6), 60.1% were males and 65.3% were Caucasians (Table 1). Of the studies providing details of comorbidities, 0.10% (n = 14,003/13991921) had malignancy [3,17,21,28,44,47,48,54,56,58,59]; 0.84% (n = 11,832/1404948) hypertension [22,25,57,58], 0.59% (n = 82,109/13952904) diabetes [17,21,25,28,48,54,58,59], and 0.001% (n = 89/11225377) had history of major surgery in the past 3 months [3,17,21,54]. Singh et al. only included patients with a diagnosis of type 2 diabetes mellitus and concomitant non-alcohol fatty liver disease (NAFLD) [25].

3.2. Incidence

Eighteen studies reported cumulative incidence per year [3,17,21,22,24,25,27,44–48,51,52,54,55,57–59], comprising a total of 1,628,164 participants, and 17,424 new VTE events in hospitalised CLD patients. Three studies reported incidence rate (person-years) [51,57,58]. Enger et al. [57] reported incidence separately for cirrhosis and CLD.

The per year cumulative incidence of VTE varied from 0.20% (95% CI 0.05, 0.51) to 8.59% (95% CI 4.78, 13.99) across the studies. Weighted average: cumulative incidence of VTE in hospitalised CLD patients by random effects meta-analysis was 1.07% (95% CI 0.80, 1.38) per year (Fig. 2a), and incidence rate was 157.15 (95% CI 14.74, 445.29) per 10,000 person-years (Fig. 2b). There was a statistically significant heterogeneity (I^2 99%, $p < 0.01$), and publication bias towards studies reporting significant results or increased risk ($p < 0.0001$) (Fig. 3).

Weighted average cumulative incidence of DVT was 0.76% (95% CI 0.41, 1.20) per year, varying from 0.10% (95% CI 0.01, 0.36) to 7.36% (95% CI 3.86, 12.51) across the nine studies. (SP-Fig. 1).

Weighted average cumulative incidence of pulmonary embolism (PE) was 0.31 (95% CI 0.06,0.72) per year, varying from 0.10% (95% CI

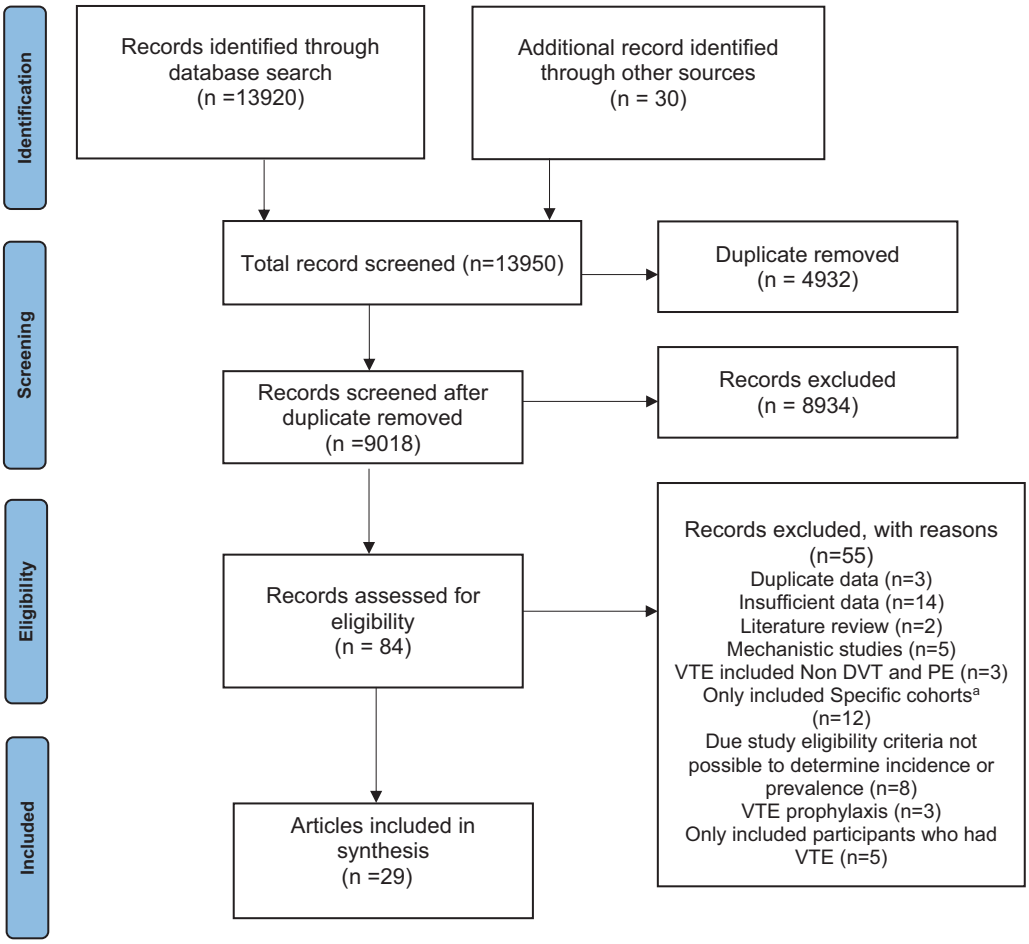

Fig. 1. PRISMA flow diagram for studies selection.
(VTE-venous thromboembolism, DVT-deep vein thrombosis, PE-pulmonary embolism, HCV-hepatitis c virus, HBV, hepatitis b virus, ITU-intensive care unit).
[a]Post trauma, post knee arthroplasty, post hip replacement, post infection, over age of 65 years, patient dies of PE, patient on chemotherapy, patient with any alcohol related health condition, ITU only patients, Patient with HCV/HBV infection and on treatment.

0.001, 0.36) to 1.23% (95% CI 0.15, 4.36) across the seven studies. (SP-Fig. 2).

3.3. Prevalence

Thirteen studies reported period prevalence per year [12,14,22,23,26,28,29,48–50,55,56,59], comprising a total of 17,533,466 hospitalised CLD patients had 134,646 pre-existing VTE events. Period prevalence of VTE in CLD varied from 0.33% (95% CI 0.23, 0.46) to 4.69% (95% CI 2.45, 8.04) per year.

Weighted average period prevalence of VTE in hospitalised patients with CLD was 1.10% (95% CI 0.85, 1.38) per year. There was statistically significant heterogeneity between studies (I^2 100%, $p < 0.01$) (Fig. 4) and publication bias ($p \leq 0.04$) (Fig. 5).

Weighted average period prevalence of DVT was 1.44% (95% CI 0.79, 2.27) per year, with a range of 0.35 (95% CI 0.14, 0.72) to 4.69 (95% CI 2.45, 8.04) (SP-Fig. 3).

Weighted average period prevalence of PE was 0.24% (95% CI 0.10, 0.44) per year (SP-Fig. 4).

3.4. Cases versus control

Eight studies reporting cumulative per year incidence were included in cases versus control meta-analysis. Weighted average RR of cumulative per year incidence of VTE in hospitalised participants with CLD compared to those without CLD was 1.55 (95% CI 0.98, 2.45) (SP-Fig. 5a).

Three studies reporting incident rate were included in cases versus control meta-analysis. Weighted average RR of incidence rate of VTE in chronic liver disease to those without CLD was 2.11 (95% CI 1.35, 3.31) (SP-Fig. 5b).

Two studies [21,54] comprising 1644 participants, provided details on VTE events in hospitalised patients with CLD on VTE pharmacological prophylaxis ($n = 441$) versus those not on VTE pharmacological prophylaxis ($n = 1203$). 1.13% ($n = 5/441$) on VTE prophylaxis had a VTE event compared to 3.08% not on VTE prophylaxis. On conducting fixed effects meta-analysis, hospitalised patients with CLD not on VTE prophylaxis were 2.78 times (RR 2.78, 95% CI 1.11, 6.98) more likely to have VTE during hospital stay compared to those on VTE prophylaxis. Heterogeneity between studies was not significant (I^2 0%, $p = 0.67$).

Data was insufficient to conduct meta-analysis on incidence and prevalence of VTE based on study setting (community versus in-hospital).

3.5. Subgroup analysis

A summary of subgroup analysis is provided in Table 2.

3.5.1. Study region

Weighted average cumulative incidence of VTE in studies undertaken in Europe/USA ($n = 14$) was 1.12% (95% CI 0.82, 1.47) per year, and in studies undertaken in Asia (n = 4) was 0.89% (95% CI 0.36, 1/61) per year. Weighted average period prevalence of VTE in Europe/USA was 1.04% (95% CI 0.77, 1.35), and in Asia was 1.39% (95% CI 0.81, 2.11) per year. Difference in incidence or prevalence of VTE between Europe/USA and Asia was non-significant ($p = 0.58$ and $p = 0.21$, respectively).

Table 1
Characteristics of included studies.

Study ID	Country	Recruitment period	Cohorts	Incidence/Period prevalence	Events[a] (n)/Cohort[b] (n)	Sex (male)	Age (years)	Ethnicity (white)
Northup 2006	USA	1993–2001	Cirrhotic	Cum incidence[c]	113/21000	–	–	–
Gracia-Fuster 2008	Spain	1992–2007	Cirrhotic	Cum incidence	17/2074	–	–	–
Gulley 2008	USA	1995–2005	Cirrhotic	Cum incidence	18/963	655	50.5	578
Lizarraga 2010	USA	2004–2008	Cirrhotic	Cum incidence	108/14790	–	–	–
Dabbagh 2010	USA	2000–2007	CLD	Cum incidence	12/190	121	50.7	–
Lesmana 2010	Indonesia	2004–2007	Cirrhotic	Period prevalence[c]	12/256	164	60.5	–
Gagan 2010*	USA	2007–2007	Cirrhotic	Period prevalence	2915/560503	–	–	–
Wu 2010	USA	1998–2006	Cirrhotic	Period prevalence	5288/649879	397,926	57.9	433,002
Aldawood 2011	KSA	2009–2009	Cirrhotic	Cum incidence	6/226	140	63	0
Ali 2011	USA	2005–2005	Cirrhotic	Period prevalence	8248/449799	275,079	–	230,536
Saleh 2011	USA	1979–2006	CLD	Period prevalence	72,000/9492000	5,678,000	56	6,250,240
Ahmed 2012*	USA	2000–2009	CLD	Incidence rate[d]	149/47391	28,908	–	–
Girleanu 2012	Romania	2010–2011	Cirrhotic	Cum incidence	31/3108	–	–	–
Kohsaka 2012*	Japan	–	Cirrhotic	Cum incidence	10/719	215	58.9	0
Barclay 2013	USA	2008–2011	CLD	Cum incidence	12/1518	1074	49.8	–
Walsh 2013	USA	2006–2010	CLD	Cum incidence	17/2606	–	–	–
				Period prevalence	27/2606	–	–	–
Ponziani 2013*	Italy	1982–2012	Cirrhotic	Period prevalence	34/10359	–	–	–
Bogari 2014	USA	2010–2013	CLD	Cum incidence	14/163	106	54	83
Enger 2014	USA	2000–2006	Cirrhotic	Incidence rate	76/15158	9102	56.5	6043
			CLD (HCV)		68/22733	14,191	49	9983
Ng 2015	Taiwan	2007–2010	Cirrhotic	Incidence rate	26/2779	1836	59	0
Yang 2015	Singapore	2004–2011	CLD	Period prevalence	102/6372	2288	53.4	0
Zang 2016	China	2011–2013	Cirrhotic	Cum incidence	4/2006	1330	56.2	0
			Cirrhotic	Period prevalence	9/2006			
Tak 2017*	India	2016–2017	Cirrhotic	Period prevalence	6/365	58.5	296	0
Barba 2018	Spain	2005–2014	CLD	Cum incidence	5623/324076	224,359	65.2	
Kasarala 2018*	USA	2005–2014	Cirrhotic	Period prevalence	14,422/1030164	–	–	–
Singh 2019	USA	2000–2015	CLD (NAFLD)	Cum incidence	71/1295	454	55.2	1102
Greenberg 2019*	USA	2003–2014	Cirrhotic	Cum incidence	11,049/1165369	–	–	–
Yassine 2020*	USA	2015–2019	Cirrhotic	Period prevalence	5179/157400	86,220		124,020
Elkafrawy 2020*	USA	2004–2014	Cirrhotic	Period prevalence	26,404/5171757	–	–	–

Mean age, n-number, CLD-chronic liver disease, HCV-hepatitis c virus, NAFLD-non-alcoholic fatty liver disease, KSA- Kingdom of Saudi Arabia.
All included studies were of observational design and done in hospital setting. Sing et al.; (2019) did not specify the study setting.
[a] Events- number of cases had venous thromboembolism (Deep vein thrombosis (DVT) and/or Pulmonary embolism (PE)).
[b] Cohort -total number of participants.
[c] Cumulative incidence and period prevalence per year.
[d] Incidence rate (person years).
* Abstract only publications.

3.5.2. Sample size

Weighted average cumulative incidence of VTE in studies of sample size greater than 10,000 was 0.74% (95% CI 0.41, 1.15) per year, and in studies recruited less than 10,000 participants was 1.33% (0.95, 1.76) per year. Weighted average period prevalence of VTE in studies of cohort size greater than 10,000 was 1.04% (95% CI 0.76, 1.36) per year, and in studies recruited less than 10,000 participants was 1.29% (95% CI 0.80, 1.88) per year. Weighted average cumulative incidence of VTE was significantly ($p = 0.02$) lower in studied of cohort size greater than 10,000, whereas there was no significant (p0.29) difference in prevalence between subgroups.

3.5.3. Study quality

Weighted average cumulative incidence of VTE in studies of low quality was 0.70% (95% CI 0.26, 1.33), in medium quality was 2.18% (95% CI 1.18, 3.45), and in high quality study was 1.14% (95% CI 0.61, 1.83) per year. Difference between subgroups based on study quality was statistically significant ($p = 0.03$). Weighted average period prevalence of VTE in studies of low quality was 1.15% (95% CI 0.86, 1.47) per year. Data was insufficient to calculate pooled period prevalence for high and medium quality studies.

3.5.4. Sex

Weighted average cumulative incidence of VTE in CLD in female participants was 4.99% (95% CI 1.84, 9.35), and in male participants was 4.60% (95% CI 3.02, 6.47) per year. As studies included to pool cumulative incidence based on sex had reported higher risk incidence of VTE in CLD hence the effect size was higher.

Weighted average period prevalence of VTE in CLD in female participants was 1.08% (95% CI 0.38, 2.07) and in male participants was 1.25% (95% CI 0.53, 2.23) per year. Difference in incidence or prevalence based on sex was non-significant ($p = 0.30$, $p = 0.87$).

3.6. Sensitivity analysis

The results of sensitivity analysis are summarised in Table 3.

Despite undertaking multiple restricted analysis based on; studies published up to 2010 or after 2010, studies with a sample size >10,000 or < 10,000, abstract only publications or full text publications, and included studies provided information on associated malignancy or missing information. It was not possible to remove residual heterogeneity.

3.6.1. Outlier studies

Studentized residual tests, Buajat plot and r diagnostic tests for influential studies confirmed three studies [3,21,25] significantly influenced the incidence meta-analysis results (SP-Fig. 6), and two studies [28,48] prevalence meta-analysis results (SP-Fig. 7).

For incidence, on excluding Singh et al. (2019) [25] from meta-analysis, weighted average cumulative incidence per year of VTE in hospitalised CLD patients was 0.92% (95% CI 0.67, 1.21) (SP-Fig. 8a). On excluding Singh et al. (2019) and Bogari et al. (2014) [21,25] weighted average cumulative per year incidence of VTE was 0.85% (95% CI 0.61, 0.97) (SP-Fig. 8b). On excluding all three studies

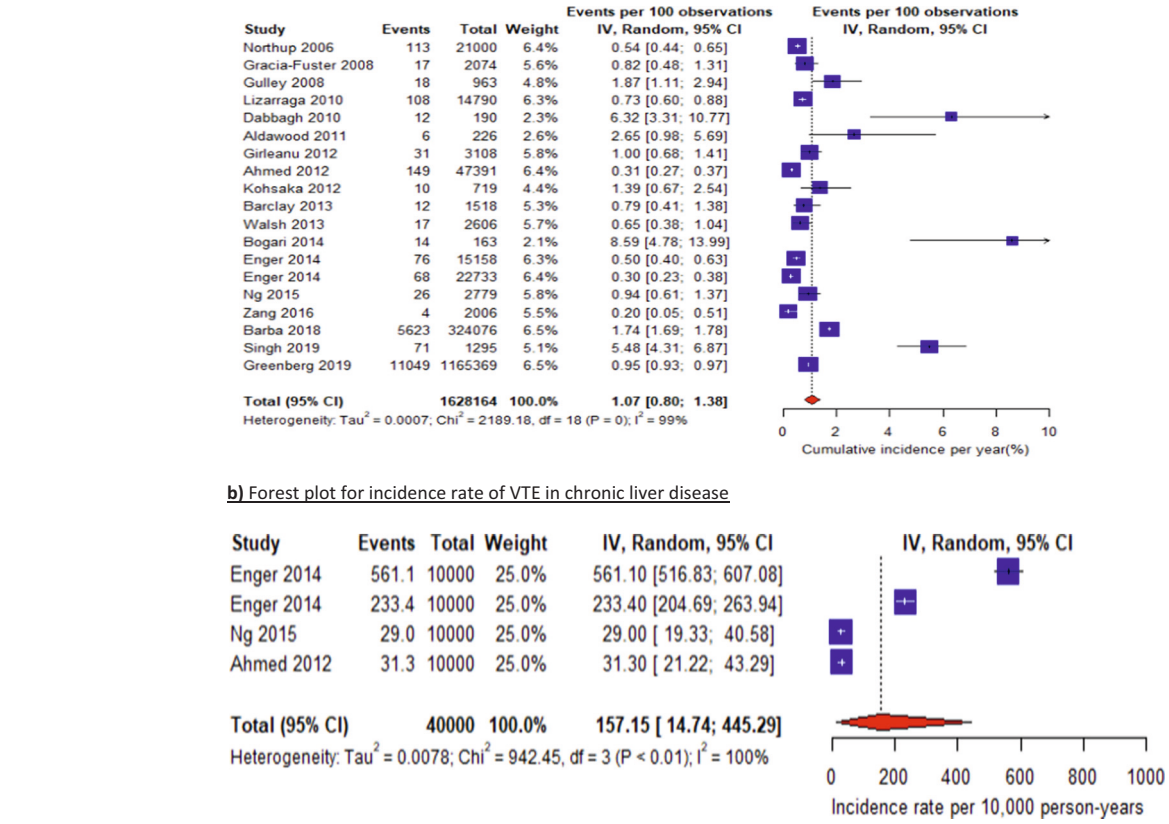

Fig. 2. Forest plots for incidence metanalysis **a)** Cumulative per year incidence of venous thromboembolism in chronic liver disease **b)** Incidence rate of venous thromboembolism in chronic liver disease.

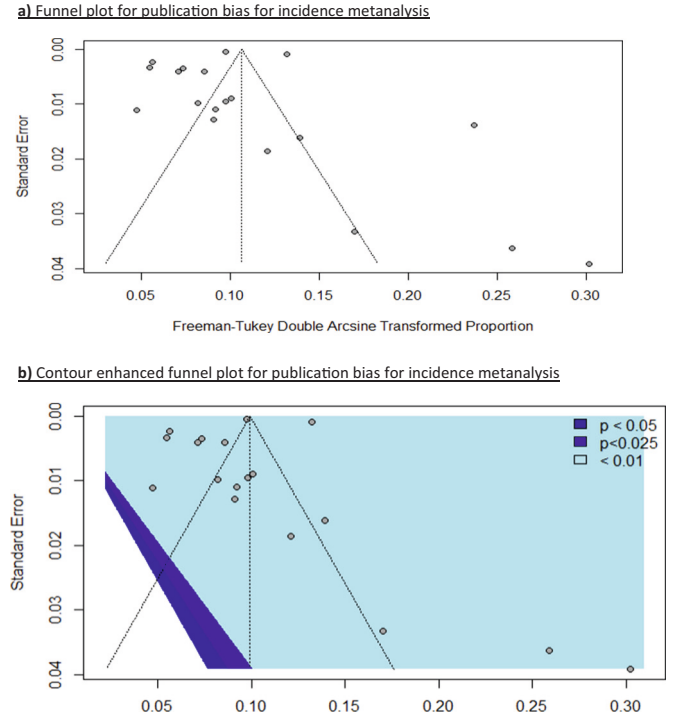

Fig. 3. Publication bias for incidence metanalysis **a)** Funnel plot **b)** Contour enhanced funnel plot.

[3,21,25] weighted average cumulative per year incidence of VTE was 0.79% (95% CI 0.55, 1.06) (SP-Fig. 8c). The residual heterogeneity remained significant.

For prevalence meta-analysis, on excluding Yassine et al. (2020) [28] weighted average period prevalence was 0.93% (95% CI 0.72, 1.16) per year (SP-Fig. 9a). On excluding both studies [28,48] weighted average period prevalence was 0.88% (95% CI 0.68, 1.11) per year (SP-Fig. 9b). The residual heterogeneity remained significant.

3.7. Meta-regression

For incidence: on univariable meta-regression analysis, quality of included study (low, medium, high), and sample size (greater than 10,000 versus less than 10,000) significantly ($p = 0.03$, $p = 0.02$, respectively) influenced the results of meta-analysis. The association for age, sex, publication type and study region (Europe and USA versus Asia) was non-significant ($p = 0.90$, $p = 0.88$, $p = 0.303$, $p = 0.57$, respectively). On multivariable meta-regression analysis age, quality, and sample size of included studies accounted for (R^2) 67.40% of heterogeneity ($p < 0.001$) whereas on including age, quality, sample size, and study region into model accounted (R^2) 78.5% of heterogeneity ($p < 0.001$). Quality and sample size combined were unable to account for any residual heterogeneity.

For prevalence: on univariable meta-regression analysis for all covariates was non-significant (Table 4).

3.8. Risk of bias assessment

Quality assessment stratified eight studies as high quality, five as medium, and sixteen as low quality. The main area of concerns were inconsistencies and errors in reported data. (SP-Table 1).

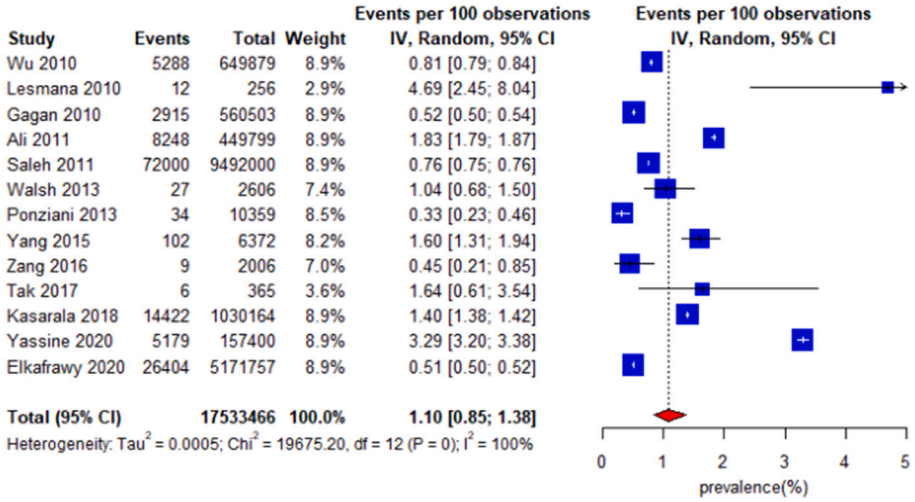

Fig. 4. Forest plot for period prevalence (per year) of venous thromboembolism in chronic liver disease.

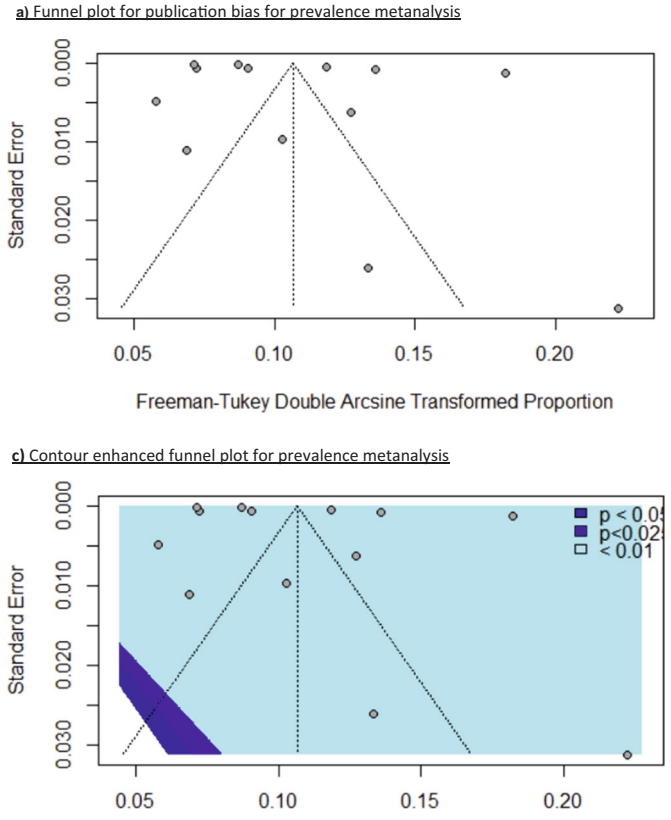

Fig. 5. Publication bias for prevalence metanalysis **a)** Funnel plot **b)** Contour enhanced funnel plot.

4. Discussion

This systematic review confirms VTE risk is significant in hospitalised patients with CLD. Twenty-nine included studies summarised the epidemiology of VTE in over 19 million CLD participants, spanning 30 years of research across 3 continents. Hospitalised CLD patients were at double the risk (RR 2.11, 95% CI 1.35, 3.31) of VTE compared to those without CLD. Meta-analysis estimates that for every 1000 hospitalised CLD patients, 10 will develop a new, and 11 a pre-existing diagnosis of VTE per year. The incidence rate was 157.15 per 10,000 person-years.

Historically, it has been argued that CLD does not increase the risk of

Table 2
Subgroup analysis.

Subgroup	Studies	Cumulative incidence (%) (per year)	Subgroup	Heterogeneity	
			P[a]	I^2 (%)	p
Study region					
Europe, USA	14	1.12(0.92, 1.47)	0.58	99.0	<0.01
Asia	4	0.89 (0.36, 1.61)		87.0	<0.01
Sample size					
>10,000	5	0.74 (0.41, 1.15)	0.02	100.0	<0.01
<10,000	13	1.33 (0.95, 1.76)		1.0	<0.01
Study quality					
Low	6	0.70 (0.26, 1.33)	0.03	98.0	<0.01
Medium	5	2.18 (1.18, 3.45)		98.0	<0.01
High	7	1.14 (0.61, 1.83)		99.0	<0.01
Sex[b]					
Female	2	4.99 (1.84, 9.35)	0.30	0.0	0.96
Male	2	4.60 (3.02, 6.47)		83.0	0.02
Subgroup	Studies	Period prevalence (%) (per year)	P[a]	I^2 (%)	p
Study region					
Europe, USA	9	1.04 (0.77, 1.35)	0.21	100.0	<0.01
Asia	4	1.39 (0.81, 2.11)		91.0	<0.01
Sample size					
>10,000	8	1.04 (0.76, 1.36)	0.29	100.0	<0.01
<10,000	5	1.29 (0.80, 1.88)		100.0	<0.01
Study quality					
Low	11	1.15 (0.86, 1.47)	0.72	100	<0.01
Medium	1	1.04 (0.29, 2.23)			
High	1	0.81 (0.22, 1.79)			
Sex					
Female	4	1.08 (0.38, 2.07)	0.87	100.0	<0.01
Male	4	1.25 (0.53, 2.23)		100.0	<0.01

% (95% confidence interval), (VTE-venous thromboembolism).
Europe n = 4, United states (USA) *n* = 18.
[a] p for significance of difference between subgroups.
[b] Fixed effects metanalysis.

Table 3
Sensitivity analysis.

Cumulative incidence per 100 patients per year					
	No. of studies	Cumulative incidence (95% CI)	I^2 (%)	Tau [2]	p (heterogeneity)
Year of publication					
Before 2010	5	1.15 (0.62, 1.82)	91.0	0.001	<0.01
After 2010	13	1.06 (0.75, 1.41)	99.0	0.001	<0.01
Sample size					
>10,000	5	0.74 (0.41, 1.15)	100.0	0.001	<0.01
<10,000	13	1.33 (0.95, 1.76)	95.0	0.001	<0.01
Publication type					
Full text	15	1.26 (0.84, 1.76)	99.0	0.002	<0.01
Abstract only	3	0.78 (0.18, 1.77)	99.0	0.002	<0.01
Malignancy					
Information provided	8	0.58 (0.37, 0.84)	91.0	0.003	<0.01
Information missing	11	1.38 (0.99, 1.83)	99.0	0.001	<0.01

Period prevalence per year					
	No. of Studies	Period prevalence (95% CI)	I^2 (%)	Tau [2]	p (heterogeneity)
Year of publication					
Before 2010	3	0.97 (0.47, 1.63)	100.0	0.001	<0.01
After 2010	10	1.14 (0.85, 1.48)	100.0	0.001	<0.01
Sample size					
>10,000	8	1.04 (0.76, 1.36)	100.0	0.001	<0.01
<10,000	5	1.29 (0.80, 1.88)	88.0	0.001	<0.01
Publication type					
Full text	7	1.21 (0.74, 1.80)	100.0	0.001	<0.01
Abstract only	6	1.06 (0.59, 1.65)	100.0	0.001	<0.01
Malignancy					
Information provided	5	1.61 (0.36, 3.68)	99.0	0.005	<0.01
Information missing	8	0.95 (0.70, 1.22)	100.0	0.003	<0.01

Table 4
Meta-regression analysis.

Variables	I^2	tau	Tests of moderator		p (heterogeneity)
			Coefficient	p	
Cumulative incidence meta-regression					
Age	96.00%	0.043	0.013	0.908	<0.001
Sex					
Male (%)	96.80%	0.036	0.019	0.889	<0.001
Female (%)	96.90%	0.036	0.100	0.751	<0.001
Quality of studies	98.70%	0.038	6.981	0.031	<0.001
Sample size	99.10%	0.027	5.502	0.020	<0.001
Publication type	86.70%	0.038	1.058	0.303	<0.001
Study region	99.20%	0.027	0.308	0.578	<0.001
Period prevalence meta-regression					
Age	94.40%	0.017	0.756	0.385	<0.001
Sex					
Male (%)	99.88%	0.041	1.22	0.269	<0.001
Female (%)	99.88%	0.041	1.19	0.274	<0.001
Quality of studies	99.95%	0.022	0.645	0.724	<0.001
Sample size	99.94%	0.021	1.101	0.293	<0.001
Publication type	99.94%	0.031	0.192	0.661	<0.001
Study region	99.94%	0.021	1.592	0.207	<0.001

Liver disease included cirrhosis or chronic liver disease unspecified of unspecified stage.
Publication type included full text and abstract only.

VTE and CLD patients may be less likely to develop VTE [60,61]. Our findings are consistent with most recent nationwide studies confirming CLD considerably increases the risk of VTE [15,58]. Estimated cumulative incidence of VTE in CLD was higher than that reported by Qi et al. (2014), but lower than the values reported by Ambrosino et al. [2,20]. In-hospital VTE in CLD constitutes up to a tenth of the burden of in-hospital VTE [17,18]. Moreover, hospitalisation, periods of immobility and hepatic synthetic dysfunction significantly increase the risk of VTE in cirrhosis [12,62].

Our results show that hospitalised CLD patients without VTE pharmacological prophylaxis were twice (RR 2.78, 95% CI 1.11, 6.98) as likely to develop VTE compared to those receiving prophylaxis. Special attention should be paid while generalising these findings as the search strategy was not customised to search for studies discussing the role of VTE prophylaxis in CLD. Moreover, there is paucity in available evidence on the effectiveness of VTE prophylaxis in CLD, and the results are conflicting, although most researchers agrees it does not increase the risk of bleeding [21,40,54,63].

Subgroup analysis demonstrated that though there was no significant difference in the cumulative incidence of VTE in hospitalised CLD patients across Europe, USA, and Asia, the period prevalence was significantly higher in Asia. Studies with a smaller cohort (<10,000) reported higher estimated cumulative incidence (1.33/100) compared to studies with a larger cohort (0.74/100). There was no significant difference in estimated cumulative incidence and period prevalence of VTE in CLD between male and female participants. Subgroup analysis findings were consistent with previous systematic reviews [20].

Pulmonary embolism (PE) compared to deep vein thrombosis carries significantly higher risk of mortality in cirrhosis [15]. 30-day mortality in hospitalised patients with PE and cirrhosis has been reported as high as 35%, compared to 7% in patients with DVT and cirrhosis. PE is among the leading causes of preventable death in hospitalised patients [64]. This review confirms cirrhotic patients are at increased risk of both DVT and PE. Clinicians treating such patients need to be alert to the VTE risk in liver disease to prevent avoidable deaths.

We followed a robust methodology in study selection criteria and data analysis to strengthen our findings. Three studies [15,65,66] included in previous systematic reviews [2,20] were excluded due to missing data or due to inclusion of very specific populations, such as, only trauma patients or patients with international normalise ratio (INR) >1.4. For the cases versus control analysis, we paid special attention to only include studies with similar control conditions to minimise the impact of confounders and bias. Furthermore, we included nine additional studies [21–29], comprising over seven million participants and sixty thousand VTE events, that were not included in any of previous reviews [2,20]. Two of these studies [21,24] were of high, and one [25] of medium quality.

Significant heterogeneity between studies was noted in most of our meta-analyses, which is a limitation, and hence a random effects method was used. Subgroup analyses and meta regression were undertaken to ascertain the sources of heterogeneity. Cohort size, study region and

type of CLD (cirrhosis vs unclassified) were found to be the sources of significant heterogeneity. Secondly, as per protocol, we aimed to compare epidemiology of VTE in CLD in community versus in-hospital settings. Despite adopting an inclusive search strategy, none of the included studies were done in a community setting. This is a recurring issue that has been noted in the previous systematic reviews [2,18,20]. Furthermore, a significant proportion of CLD patients remain undiagnosed until their first hospital admission [67], which makes it harder to determine the epidemiology of VTE in CLD in community settings. Thirdly, none of the included studies were from Africa, Australia, or South America, which limits the generalisability of this review to these populations. All studies included were of observational design, which inherently increases the risk of bias, such as selection and information bias, which might have under- or overestimated the results [68]. To address any potential source of uncertainty in the results a sensitivity analysis involving subgroup analyses and meta-regression was undertaken. Several studies included in the current meta-analysis had participants with a history of malignancy. As malignancies can significantly increase the risk of VTE, this may have influenced the estimated incidence of VTE in liver disease [69]. Considering malignancy is a prothrombotic condition [70] a meta-analysis on studies providing or missing details on associated malignancies was conducted. Only seven studies reporting cumulative incidence, and five studies reporting period prevalence provided information on associated malignancies. Due to limited information on associated malignancies, and with none of the included studies investigating incidence or prevalence of VTE in CLD in the absence or presence of malignancy, it was not possible to precisely ascertain the effect of malignancy in CLD on risk of VTE. HCC independent of cirrhosis or stage of liver disease increases the risk of venous thromboembolism [71,72]. Whereas the focus of the current systematic review was to evaluate the increased risk of VTE due to the systemic effect of cirrhosis. In this view, the studies where the cohort was purely consistent of patients with HCC were excluded. Moreover, most of the included studies were missing details on other comorbidities which could increase the risk of VTE. Keeping this in view a dedicated cases (patient with CLD and VTE) versus control (patient without CLD but had VTE) analysis was conducted. Lastly, due to insufficient data it was not possible to ascertain risk of VTE based on underlying aetiology or stage of CLD. As cirrhosis and its association with portal vein thrombosis (PVT) is well described and studied, factors affecting PVT are in part explained by changes in portal circulation [73]. Increased intrahepatic vascular resistance and sluggish blood flow in portal vein in cirrhosis are two important contributory factors in pathophysiology of PVT [73]. While focus of the current systematic review was to study the systemic effect of cirrhosis, hence we excluded PVT from analysis. Lastly, due to insufficient data, it was not possible to conducted separate subgroup analysis to report the risk of VTE based on severity (MELD or Child Pugh score) of liver disease.

The findings of this review have clinical implications. A VTE event complicating CLD is likely to increase the risk of morbidity, mortality and prolong hospital stay [14,17]. Healthcare services are already spending over 1% of their budget in treating CLD, any further in hospital events significantly increase the economic burden [74,75]. Despite a significant risk of VTE in CLD, only 26.8% of hospitalised patients were on pharmacological prophylaxis. A recent literature review reported over 76% of hospitalised patients with cirrhosis did not receive either pharmacological or mechanical VTE prophylaxis [76]. It highlights the importance of thrombosis in hospitalised patients with cirrhosis and strongly suggests that universal VTE prophylaxis should be prescribed. This will require a "cultural shift" given the ingrained views of doctors caring for CLD patients that the major risk is haemorrhage. Studies have shown pharmacological VTE prophylaxis to be safe in CLD and reduce the incidence of VTE [41,77]. The most recent Baveno consensus (Baveno VII), European Association for the Study of the Liver (EASL) and American Gastroenterology Association (AGA) guidelines emphasise on personalising the care in portal hypertension and advocate for thromboprophylaxis to reduce the risk of venous thrombosis in cirrhosis [8,78,79].

In conclusion, our results show hospitalised patients with underlying CLD may exhibit an increased risk of developing VTE (DVT and/or PE); for every 1000 hospitalised patients with CLD, 10 will develop a new, and 11 will have a pre-existing diagnosis of VTE per year. An auto-anticoagulatory state in cirrhosis does not always protect against thrombosis. It is beyond the scope of this study to determine current practice but, anecdotally, prescribing of low molecular weight heparin (LMWH) is often withheld in cirrhotic patients. Educating healthcare professionals providing direct care to these patients will be a key driver to influence clinical practice.

CRediT authorship contribution statement

Mohsan Subhani: Contributed to protocol writing, scoping search, drafting final Search Strategy, literature search, abstract screening, data extraction including critical appraisal, meta-analysis, report writing, and proofreading final manuscript.

Abhishek Sheth: Contributed to data extraction including critical appraisal, meta-analysis, report writing, and proofreading final manuscript.

Jamal Ahmed: Contributed to data extraction including critical appraisal, report writing and proofreading final manuscript.

Pramudi Wijayasiri Contributed as the additional reviewer in literature search, abstract screening, data extraction, and proof readying manuscript.

Syed Anjum Gardezi: Contributed as the second reviewer in literature search, abstract screening, data extraction including critical appraisal, meta-analysis, report writing, and proofreading final manuscript.

Doyo Enki: Statistical support for meta-analysis, proof-reading results.

Joanne R Morling: Contributed to finalising research question, proofreading, and finalising the manuscript.

Guruprasad Aithal: Contributed to finalising research question, proofreading, and finalising the manuscript.

Stephen D Ryder: Contributed to finalising research question, proofreading, and finalising the manuscript.

Dr. Aloysious D Aravinthan: Senior Author: Contributed to finalising research question, proof-reading, developing the search strategy and protocol, statistical support, and finalising the manuscript. He also acted as 3rd reviewer in case of disagreement in primary reviewers.

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

Declaration of competing interest

No declared conflict interest from any authors.

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Alison Ashmore, senior research librarian (Nottingham University Libraries) contributed to finalising the search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2022.05.004.

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