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Efficacy and safety of the use of heparin as thromboprophylaxis in patients with liver cirrhosis: A systematic review and meta-analysis ☆

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ABSTRACT

Introduction: Venous thromboembolism is a common cause of morbidity and mortality. Although cirrhosis has classically been considered as an acquired bleeding diathesis, there is increasing evidence that rejects the traditional belief that these patients are naturally protected against venous thromboembolism. However, antithrombotic prophylaxis in this setting is still underused. The aim of this review is to assess if the use of heparin in cirrhotic patients is effective in the prevention of venous thromboembolism and whether its use is related to an increase in bleeding episodes.

Material and methods: We searched in MEDLINE and EMBASE, using the terms "liver cirrhosis", "heparin", "low molecular weight heparin," "venous thrombosis", "deep venous thrombosis", "hemorrhage" and "bleeding". We sought for clinical trials and observational studies performed in patients with liver cirrhosis to evaluate the efficacy or the safety of the heparin. It was used the *Mantel-Haenszel* method with a random effects model. Odd Ratio was the main measure of effect. The results of the pooled OR and its 95% confidence intervals were expressed in forest plots. The heterogeneity was assessed by the I^2 statistic. The statistical software RevMan was used.

Results and conclusions: The current review found that, although the use of heparin was not related to higher rates of bleeding in cirrhotic patients (pooled OR 0.87 95% CI (0.34-2.18)), it doesn´t decrease the risk of venous thromboembolism in patients receiving prophylaxis, with a pooled OR 1.65 95% (0.36 to 7.54). However, further prospective studies are needed to assess this issue.

Introduction

Cirrhosis has classically been considered as an acquired bleeding diathesis [1,2], due to most of factors that contribute to proper hemostasis are impaired (thrombocytopenia, low levels of procoagulant factors as fibrinogen, II, V, VII, IX, X, XI, and development of hyperfibrinolysis). However, this concept is currently being reviewed, since it has been observed that these patients also have several anomalies which promote thrombosis (increased levels of Von Willebrand and VIII factors, decreased levels of ADAMTS13, antithrombin, C protein and plasminogen). In fact, a new balance between anti-and procoagulant systems is set. However this balance is more unstable in cirrhotic patients than in healthy people; therefore, they can develop bleeding events or thrombosis, depending on what concurrent risk factors are present [3].

Venous thromboembolism (VTE) is a common cause of morbidity and mortality. In Spain it has been estimated an incidence of 118 cases per 100,000 inhabitants every year [4], being these figures similar to other European and North American records. Several studies have evaluated the risk of VTE in cirrhotic patients with heterogeneous results. Sogaard et al. [5] published a case-control study, which included 100,000 patients with VTE and 500,000 population controls. Patients with liver cirrhosis had a clearly increased relative risk for venous thromboembolism (RR 1.74 95% CI (1.54-1.95)). Also, another study performed in the United States that analyzed a total of 650,000 cirrhotic patients and 575,000 non-cirrhotic inpatients, found that, in patients younger than 45 years, patients with stable disease had an OR 1.23 95%CI (1, 04-1.46), increasing to 1.39 95%CI (1.15-1.69) when patients with decompensated cirrhosis were evaluated [6]. By contrast, other studies didn´t show this increased risk, but a risk similar to other inpatients [7,8]. Despite the differences between studies, there is a growing evidence that rejects the traditional idea that the coagulopathy in patients with cirrhosis is protective against VTE, and supports that these patients have a significant risk of thrombotic complications [9,10].

The incidence of VTE and its complications can significantly be reduced by prophylactic measures. However, current guidelines don't include specific recommendations for cirrhotic patients. Generally it is recommended to avoid pharmacological prophylaxis with heparin in patients at high risk of bleeding [11,12]. As mentioned above, cirrhotic

Abbreviations: VTE, venous thromboembolism; MH, *Mantel-Haenszel*; REM, random effects model; OR, Odd Ratio; CI, confidence intervals.

☆ C Gómez Cuervo was responsible of the conception of the study, the acquisition, analysis and interpretation of data, and, also, drafted the article. O Bisbal Pardo and MA Pérez-Jacoiste Asin revised it critically for important intellectual content. All the authors approve the final version to be submitted.

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patients have an abnormal hemostasis which can make them prone to thrombotic or hemorrhagic phenomena. The studies assessing the safety of anticoagulation in patients with chronic liver disease are also conflicting [13,14]. However, so far, they have always been considered at a high risk of bleeding, involving an underuse of antithrombotic prophylaxis in this setting [10,15].

The aim of this review is to assess if the use of heparin (both low molecular weight and non-fractionated) in cirrhotic patients is effective in the prevention of VTE and whether its use is related to an increase in bleeding episodes.

Material and methods

We searched in MEDLINE, through PubMed, and EMBASE from inception to the date of the search (March 20, 2013). We included the terms "liver cirrhosis", "heparin", "low molecular weight heparin," "venous thrombosis", "deep venous thrombosis", "hemorrhage" and "bleeding", both as MeSH terms as in free format. There were not limitations by language. References of relevant articles found were also reviewed manually. The authors of Dabbagh et al. [10] were contacted for raw data. A single investigator performed the review.

The inclusion criteria were the following: a) the studies must be clinical trials or observational studies (cohort and case-control), b) all the subjects included must have a previous diagnosis of liver cirrhosis from any cause and at any stage, c) the intervention must consist in the administration of any dose of heparin, d) there was a control group that did not receive heparin (no intervention, placebo, another intervention), e) it was recorded either the proportion of deep vein thrombosis or the proportion of bleeding occurred in both groups. The exclusion criteria were: a) they didn't meet the inclusion criteria, b) the data of the article were duplicated in other papers; b) it evaluated other anticoagulant treatments different from heparin; c) there weren't any control groups; c) the objectives were variables surrogates, such as laboratory measurements, instead of clinical events.

A single author assessed the quality of the articles (Table 1). The following data were extracted from the selected papers: author, year of publication, type of design, age, sex, evaluation of the bleeding risk performed, hepatocellular carcinoma prevalence, type and dosage of heparin, length of heparin therapy, existence of control group and intervention applied thereto, the number of bleeding and thrombosis recorded in both groups.

The publication bias was analyzed by funnel plots. It was decided to perform the meta-analysis using the *Mantel-Haenszel* technique (MH) with a random effects model (REM). We used the Odd Ratio (OR) as the main measure of effect for the two main objectives (proportion of bleeding episodes and proportion of venous thrombosis). The results of the pooled OR and their confidence intervals (95% CI) were expressed in forest plots. Finally, we analyzed the heterogeneity by the I^2 statistic. Data analysis was performed using the statistical software RevMan (Review Manager [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

A total of 400 citations were found, seven of them were finally selected for the review. The study of Dabbagh et al. [10] could not be included because it was not possible to contact the authors to complete the data, nor could be included the article by Huang et al. [16] for being only available in Chinese. Intagliata et al. [17] was included by suggestion of the reviewer. Fig. 1 shows the diagram of selection. The absence of significant publication bias was evaluated by performing a funnel plot (Fig. 2). It shows a symmetrical distribution of the studies that evaluated the risk of VTE and the use of heparin; by contrast, the funnel plot of the studies about the risk of bleeding is asymmetric, suggesting that there are studies not included. Therefore, and according to the initial protocol, analysis was performed by REM model.

All studies were retrospective, except those of Maruyama et al. [18] (prospective observational study) and Villa et al. [19] (randomized controlled trial). The results of these studies are shown in Tables 2 and 3. Three of them [20–22] evaluated the risk of VTE in cirrhotic patients with and without prophylaxis with heparin (Fig. 3). There was not lower risk in patients receiving prophylaxis, with a pooled OR 1.65

Table 1
Characteristics and analysis of quality of the included studies.

Author	Year	Design of study	Observations
Al - Dorzhi	2010	Retrospective cohorts	It was a presentation at a meeting, not published in a scientific journal. It was a retrospective study, being prone to an information bias. There was not a random assignment given the design, neither comparisons of baseline characteristics were made to show that both groups were homogeneous except in intervention. In fact it seems that patients who did not receive antithrombotic prophylaxis were due to have an increased risk of bleeding. The sample size was not justified. With regard to the results, they did not define or quantify episodes of bleeding.
Aldawood	2011	Retrospective cohorts	It was a retrospective study, being prone to an information bias. There was not a random assignment. They did not record the details of the intervention (type or dosage of heparin used). The sample size was not justified. Multivariate or regression techniques were not applied in order to control potential confounding factors. With regard to the results, they did not define or quantify episodes of bleeding.
Garcovich	2011	Retrospective cohorts	It was a presentation at a meeting, not published in a scientific journal. It was a retrospective study, being prone to an information bias. There was not a random assignment given the design. However, although data were not shown, they told that both groups were comparable on the basis of baseline characteristics. The exclusion criteria could limit extrapolation from the study to other populations. They did not record the details of the intervention (type or dosage of heparin). The sample size was not justified. With respect to the results, it was not designed to assess the risk of VTE.
Intagliata	2011	Retrospective cohorts	It was a presentation at a meeting, not published in a scientific journal. It was a retrospective study, being prone to an information bias. There was not a random assignment due to the design. Although data were not shown, they told that both groups had comparable baseline characteristics. However an historical control group is used, which can affect to the homogeneity between groups. They did not record the details of the intervention (type or dosage of heparin). The sample size was not justified. With respect to the results, they only reported gastrointestinal bleeding, and didn´t analyze VTE risk.
Maruyama	2012	Prospective cohorts	There was not a random assignment given the design. Study groups were not entirely comparable: the control group was cirrhotic patients without portal thrombosis, and that basal difference could affect the results. The design was prospective, so the likely of an information bias was lower and there was a protocol for the intervention. The sample size was not justified. With respect to the results, they recorded bleedings from OV, but no other bleeding complications. It was not designed to assess the risk of VTE.
Villa	2012	Clinical trial	There was a randomized assignment and sequential sampling. It was a controlled study. Masking techniques were not carried out. It was held in a single center. The exclusion criteria could limit the extrapolation of the results. The sample size for the main goal (development of PT) was justified. There was a protocol for the intervention. The analysis was made by intention to treat. It was not designed to assess the risk of VTE.
Vivarelli	2010	Retrospective cohorts	It was a retrospective study, being prone to an information bias. There was not a random assignment given the design. However, a comparison of the baseline characteristics of the two groups showed that they were not homogeneous. Multivariate or regression techniques were not applied in order to control potential confounding factors. The sample size was not justified.

VTE: venous thromboembolism; PT: portal thrombosis; OV: oesophageal varices.

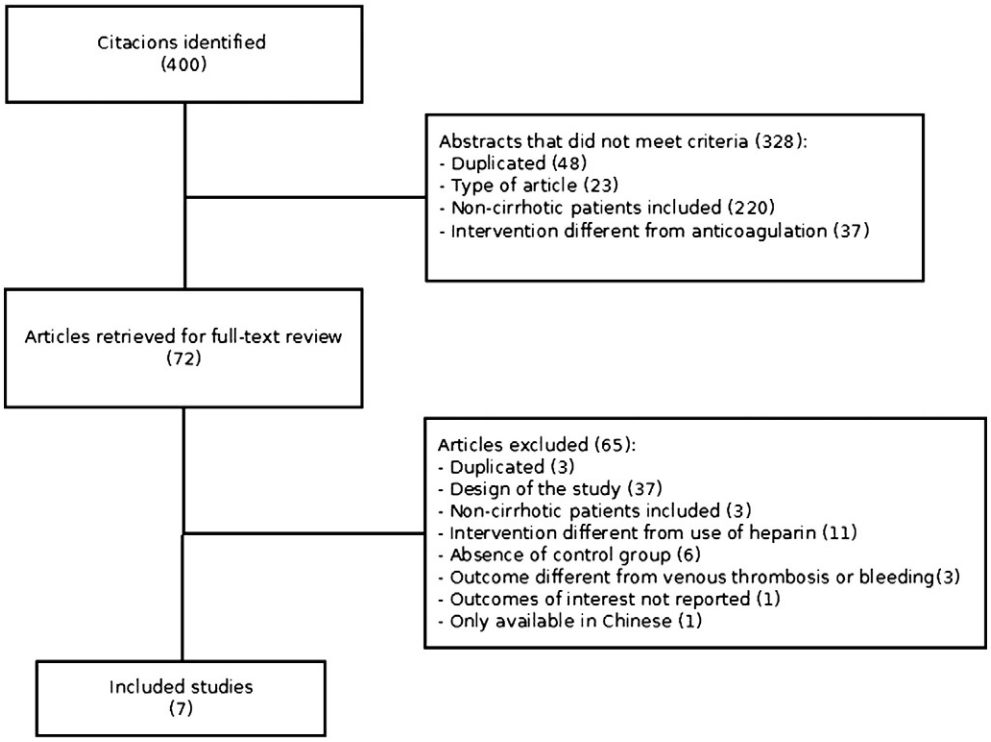

Fig. 1. Summary of evidence search and selection.

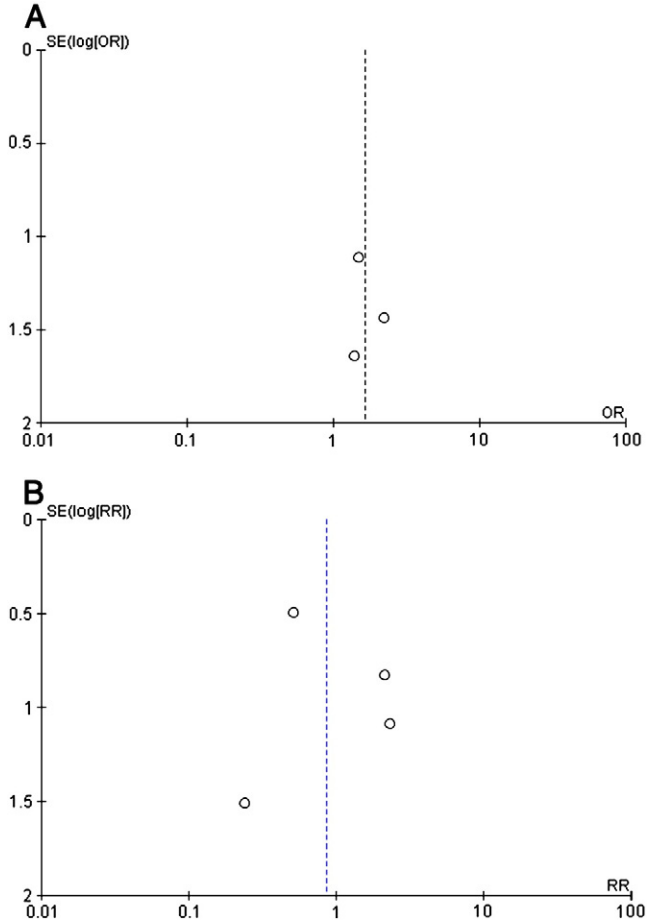

Fig. 2. A) Funnel plot for the papers which assess the risk of venous thromboembolism and the use of heparin in cirrhotic patients. B) Funnel plot for the papers which assess the risk of bleeding and the use of heparin in cirrhotic patients.

95% CI (0.36 to 7.54). Five studies [17–19,22,23] assessed the risk of bleeding in cirrhotic patients with and without use of heparin (Fig. 4). There was not higher risk of bleeding in the group receiving heparin, with a pooled OR 0.87 95% CI (0.34 to 2.18). Included studies show statistical homogeneity ($I^2 < 25\%$). Finally, only three cases of heparin–induced thrombocytopenia were reported (over a total of 627 patients treated).

Discussion

Our analysis has fail to show the effectiveness of heparin to avoid VTE in cirrhotic patients, contrary to what is described in literature for other hospitalized patients [24]. Several factors could account for this fact. First, in the three included studies [20–22] the control group could receive mechanical prophylaxis. Since the protective effect of this intervention is not quantified, it might decrease the potential benefit of heparin use. Moreover, despite its importance, the incidence of VTE is relatively low, implying the need for a larger sample size in order to evaluate the real effect of the intervention. Finally, marked clinical heterogeneity is evident, due to the different inclusion and exclusion criteria for each study. Thus, the presence of hepatocellular carcinoma was an exclusion criterion in Villa et al. [19] and Garcovich et al. [23], while Vivarelli et al. [22] study was performed in cirrhotic patients who had undergone hepatocellular carcinoma surgical resection. Dabbagh et al. [10] carried out a retrospective study including 190 patients with cirrhosis classified according to the presence of different degrees of coagulopathy, measured by levels of INR. In this study, patients in advanced stages (Child Pugh C), although related to higher INR values, showed a non-significant trend toward higher risk of VTE than subjects in earlier stages (so, the percentage of VTE episodes was: Child Pugh A 4.6%, B 4.6%, C 8%, $p = 0.602$). In our review, the different studies were also heterogeneous in terms of disease severity, not including patients with Child Pugh C in some of them [22,23]. Apart from that, some studies comprehended outpatients [23,19] while patients admitted on conventional ward [17,18,21,22] or intensive care unit [20] are included in others. This can affect the results; due to outpatients usually have lower thrombotic risk than inpatients.

Secondly, the use of heparin in cirrhotic patients was not related to an increased in bleeding episodes. Several issues have to be considered

Table 2
Results: description of the population.

Author	Inclusion criteria	Exclusion criteria	Place of attendance	Age (years)	Sex (male)	Severity of the cirrhosis	Evaluation of the risk of bleeding	HCC
Al - Dorzhi	Cirrhotic patients admitted on ICU	NS	ICU	NS	NS	NS	INR 2.2 (0.09) *	NS
Aldawood	18 years or older and a history and clinical presentation consistent with liver cirrhosis and/or a liver biopsy showing cirrhosis.	Previous anticoagulation therapy	Conventional ward	VTE group: 63.5(49-83-7); non-VTE group: 63 (54-70)**; p 0.67	VTE group: 2/6(33.3%); non-VTE group: 138/220(62.7%); p 0.57.	VTE group 6/6 (100%) Child Pugh B or C; non-VTE group: 156/220 (71%) Child Pugh B or C.	VTE group: 1.55 INR (1. 25-2.15); non-VTE group: 1.3(1.1-1.6)**; p 0.24	VTE group: 1/6(16.6%); non-VTE group: 100/220(45.5%)
Garcovich	Cirrhotic patients with PT.	Advanced liver cirrhosis (Child Pugh C), liver transplantation during follow-up, cavernomatous transformation of PT, presence of neoplasm and active variceal bleeding or high risk OV.	Outpatients	NS	NS	NS; Child Pugh C is exclusion criterion	NS; the existence of high-risk OV is exclusion criterion	HCC is exclusion criterion
Intagliat	Cirrhotic patients admitted on non-intensive care unit after an institutional policy was enacted requiring DVT prophylaxis in all inpatients without active bleeding between 2008- 2009. Historical controls were derived from the same class of patients who did not receive DVT prophylaxis and did not experience DVT from a period prior to the institution of the policy.	NS	Conventional ward	57.6 (11.3)*	299/496 (60.3%)	MELD 15.6 (7.4)*	NS	NS
Maruyama	Cirrhotic patients with OV bleeding and US examination before emergency endoscopy including a contrast study to assess the presence or absence of PT.	Cavernoma on US images, pregnancy, age younger than 16 or older than 80 years, active gastrointestinal bleeding not controlled by intensive treatment, egg allergy.	Emergency admission	PT group: 65.4 (11.4); non-PTgroup: 62.5 (12.0) *; p 0.63	PT group 3/5 (60%);non-PT group 9/18 (50%); p 0.99	PT group Child Pugh 8.6 (2.3); non-PT group 8.3 (1.7) *; 0.78 p	Patients are included after an episode of OV bleeding.	PT group: 0/15 (0%); non-PT group 3/15(20%); p 0.99
Villa	18 years or older, cirrhosis of any ethiology, a Child Pugh score between B7 and C10, absence of ascites, spontaneous bacterial peritonitis, portal hypertensive bleeding or portosystemic encephalopathy for at least three months before enrollment, and no evidence of PVT or splenomesenteric thrombosis by US evaluation or angioCT.	Older than 75 years, history of gastrointestinal bleeding, HCC, other intrahepatic/extrahepatic cancers, thromboembolic disease, ongoing anticoagulation, antiagregation or antiphospholipid antibody treatment. Pregnancy, breastfeeding, F2 varices with red whale marks or F3 varices unless ligated, platelet count less than 10.000/mm^3, evidence of HIV or PNH.	Outpatients	Group with LMWH: 56 (5); control group: 57 (7) *; p 0.56	Group with LMWH: 25/34(73.53%); control group: 26/36(72.22%)	Group with LMWH Child-Pugh 7.5 (0.9); control group 7.7 (1) *; p 0,252.	Group with LMWH: INR 1.3 (0.2); Group control 1.3 (0.3) *. Group with LMWH: previous bleeding 3/34(8,82%); control group 5/36(13,89%); p 0.51	HCC is exclusion criterion
Vivarelli	Cirrhotic patients with HCC undergoing liver resection	NS	Surgical ward	Group with LMWH: 65 (9.8); control group:63 (9.5) *; p 0.08	Group with LMWH: 119/157(75,80%); control group: 72/52 (72,22%); p 0.33	Group with LMWH: Child Pugh A 154/157(98.09%), B 3/157(1.91%); control group Child Pugh A 64/72(88.89%), B 8/72(11.11%). No patient had class C disease.	Group with LMWH: FFP transfusion during surgery 139 mL (0-1200); control group 266 mL (0-1200) **; p 0,003	HCC is inclusion criterion: 229/229 (100%)

VTE: venous thromboembolism; LMWH: low weight molecular heparin; HCC: hepatocellular carcinoma; ICU: intensive care unit; NS: not specified; FFP: frozen fresh plasma; PT: portal thrombosis; OV: oesophageal varices, HIV: human immunodeficiency virus; PNH: paroxysmal nocturnal hemoglobinuria.

* mean (standard deviation).

** median (range).

Table 3
Results: intervention and number of events.

Author	Objective	Intervention	Control	Length of heparin therapy	Definition of event	VTE		Bleeding		Follow up
						Intervention	Control	Intervention	Control	
Al - Dorzhi	Assess the risk of DVT and quantify the use of prophylaxis.	Heparin (UFH 23/1 LMWH)	No treatment/ mechanical prophylaxis	NS	DVT: 'clinically' detected It did not define bleeding	1/24	1/52	NS	NS	Until death or 5 days after discharge from the ICU
Aldawood	Determine the incidence of VTE in hospitalized cirrhotic patients and evaluate the use of prophylaxis in this population	Heparin (UFH/LMWH)	No treatment/ mechanical prophylaxis	NS	Symptomatic DVT or PE confirmed by venous doppler ultrasound of the lower limbs or spiral CT or a high probability ventilation-perfusion scan. It did not define bleeding	1/27	5/199	NS	NS	NS
Garcovich	Resolution of PT	LMWH	No treatment	For 3-6 months or until resolution of PT	Uncontrollable bleeding. It did not define VTE	NS	NS	0/15	0/15	Between 3-6 months
Intagliata	Safety of prophylactic heparin in cirrhotic patients	Heparin	No treatment	4.7(4.6)* days	Gastrointestinal bleeding. Standardized definitions for VTE (not explained)	5/355	NS	9/355	7/141	NS
Maruyama	Resolution of PT and safety of heparin	LMWH (75 IU/kg/day)	No treatment	NS	OV bleeding. It did not define VTE	NS	NS	0/15	2/18	Medium: 351 days
Villa	Efficacy of LMWH for PT prophylaxis	LMWH (enoxaparin 4000 IU/day)	No treatment	48 weeks	OV bleeding. Minor bleedings (epistaxis).	NS	NS	4/34	2/36	LMWH group 89 (57) weeks; control group 58 (37) weeks *
Vivarelli	Efficacy and safety of the use of prophylactic LMWH in cirrhotic patients with HCC	LMWH and mechanical prophylaxis (Nadroparin 0.3 mL or enoxaparin 0.4 mL subcutaneous)	Mechanical prophylaxis	Seven days from the day of surgery or until patient was actively ambulant	VTE: Symptomatic or asymptomatic DVT or PE confirmed by venous Doppler ultrasound of the lower limbs or angio- CT. Bleeding: blood loss through surgical drainage associated with a drop of 1.5 g/dL in the HB levels; intra-abdominal blood-density collection larger than 3 cm in CT; gastrointestinal bleeding.	1/157	0/72	5/157	1/72	Up to 12 months.

VTE: venous thromboembolism; HB: hemoglobin; LMWH: low weight molecular heparin; HCC: hepatocellular carcinoma; UFH: unfractionated heparin; NS: not specified; CT: computed tomography; PE: pulmonary embolism; PT: portal thrombosis; DVT: deep vein thrombosis; ICU: intensive care unit; OV: oesophageal varices.
* mean (standard deviation).

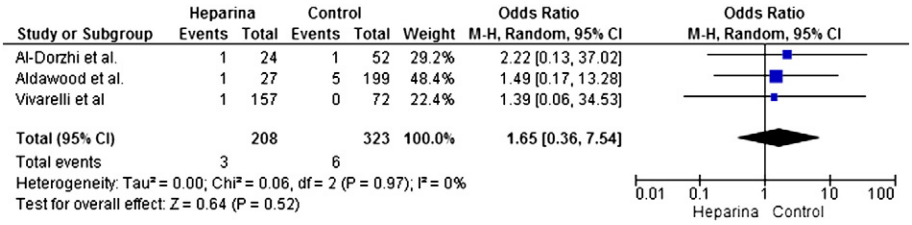

Fig. 3. Forest plot: pooled OR for the risk of venous thromboembolism in relation to the use of heparin in cirrhotic patients.

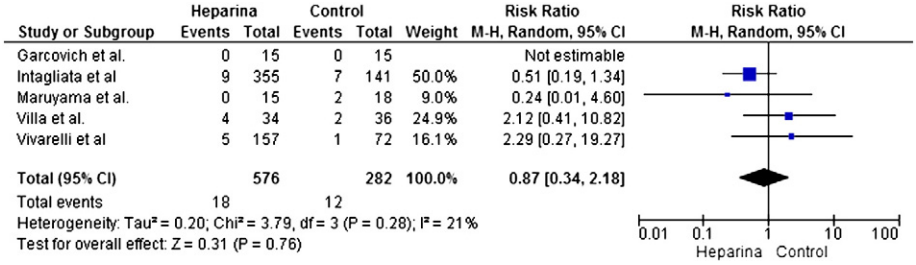

Fig. 4. Forest plot: pooled OR for the risk of bleeding in relation to the use of heparin in cirrhotic patients.

to explain this result: a) none of the included studies had the risk of bleeding as the main objective, b) there was a different assessment of the bleeding risk between the studies and, given that most of the included studies didn't have a randomized assignment, those patients with a higher perceived risk did not receive heparin, c) the type and dosage of heparin were different in each study, d) it was likely that minor bleedings or those with no significant clinical repercussions were not registered. The result found is consistent with what is shown in studies in non-cirrhotic patients [24]. In patients with liver cirrhosis, García-Fuster et al. [14] evaluated the safety of heparin for the treatment of VTE, showing a higher rate of bleeding complications in those receiving anticoagulation (14/17, of which 6 were considered severe by requiring blood transfusions). However, it should be noted that the majority (5/6) of severe forms occurred in patients who were being treated with both heparin and acenocoumarol. On the other hand, there are several studies [13,25] about the use of heparin in cirrhotic patients who developed portal thrombosis. These papers haven't found a significant increase in bleeding episodes. Therefore, the use of heparin in these patients seems safe.

Despite to the above limitations, up to date, studies addressing this issue are scarce and small in size. The current review can serve as a starting point for future research, being still needed larger prospective studies to assess the efficacy and safety of heparin as antithrombotic prophylaxis in cirrhotic patients.

Conflict of interest

None.

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