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Liver stiffness and platelet count for identifying patients with compensated liver disease at low risk of variceal bleeding

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Abstract

Background & Aims: The 2015 Baveno VI guidelines recommend against performing upper gastrointestinal endoscopy in patients with compensated cirrhosis who have a liver stiffness <20 kPa and a platelet count >150 000/mm³ because of a low prevalence of varices at risk of bleeding in this population. The aim was to synthesize the available evidence on the usefulness of the combined use of liver stiffness and platelet count to identify patients without oesophageal varices.

Methods: Meta-analysis of trials evaluating the usefulness of a given cut-off for liver stiffness and platelet count to rule out the presence of oesophageal varices.

Results: Fifteen studies were included. All studies excepting five used the Baveno VI criteria. Compared to patients with either high liver stiffness or low platelet count, those with low liver stiffness and normal platelet count had a lower risk of varices at risk of bleeding (OR=0.22, 95% CI=0.13-0.39, *P*<.001) with low heterogeneity between studies (I^2=21%). They also had a lower risk of varices (OR=0.23, 95% CI=0.17-0.32, *P*<.001) with moderate heterogeneity between studies (I^2=28%). In patients with low liver stiffness and normal platelet count, the pooled estimate rates for varices at risk of bleeding was 0.040 (95% CI=0.027-0.059) with low heterogeneity between studies (I^2=3%).

Conclusions: Patients with low liver stiffness and normal platelet count have a lower risk of varices than those with either high liver stiffness or low platelet count. Varices at risk of bleeding are found in no more than 4% of patients when liver stiffness is <20 kPa and platelet count is normal.

KEYWORDS

Child–Pugh score, cirrhosis, liver stiffness, oesophageal varices, platelets count, portal hypertension

1 | INTRODUCTION

In recent years, numerous efforts have been made to predict the presence of oesophageal varices by non-invasive means in patients with compensated cirrhosis. Liver stiffness measurement and indirect markers of portal hypertension such as platelet count have been correlated with the severity of portal hypertension and have been used to predict the presence of varices.[1-5] During the 2015 Baveno Consensus Workshop on portal hypertension, the combined use of a liver stiffness <20 kPa and a platelet count >150 000/mm³ was proposed as a new criterion for selecting patients with compensated cirrhosis who have a low risk of varices at risk of bleeding.[6] For this

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CI, confidence interval; EASL, European Association for the Study of the Liver; NA, not available; NAFLD, non-alcoholic liver disease; OR, odd ratio.

reason, the Baveno VI guidelines recommend that patients with both these criteria do not require upper gastrointestinal endoscopy.

Although several studies have indicated that patients with a transient elastography <20 kPa and a platelet count >150 000/mm³ had a low risk of presenting oesophageal varices and an even lower risk for varices at risk of bleeding,[7-9] some studies did not reach that conclusion.[10,11] This difference may have been due to a limited sample size resulting in insufficient statistical power. As a result, the magnitude of the difference in the risk of presenting varices between patients fulfilling Baveno VI criteria and those who do not fulfill these criteria remains unsettled and rigorous analysis of all available data from all studies is required. More particularly, a precise estimate of the prevalence of varices at risk of bleeding in patients with liver stiffness <20 kPa and platelet count >150 000/mm³ is necessary before a recommendation to renounce performing endoscopy is applied in all patients with compensated cirrhosis.

Meta-analysis is a quantitative technique that enables pooling data from trials in order to decrease random errors. It also allows for assessment of a particular factor's impact magnitude. In this study, we performed a meta-analysis of trials evaluating the usefulness of the combined use of liver stiffness and platelet count to rule out the presence of varices among patients with compensated cirrhosis. Our objective was to compare the risk of finding varices and the risk of finding varices at risk of bleeding among patients with low liver stiffness and normal platelet count compared to patients with either high liver stiffness or low platelet count. We also aimed to assess the rate of varices and the rate of varices at risk of bleeding among patients with low liver stiffness and normal platelet count, particularly among those with a liver stiffness <20 kPa and a platelet count >150 000/mm³.

Key points

- The 2015 Baveno VI guidelines recommend to cancel upper gastrointestinal endoscopy in patients with liver stiffness <20 kPa and a platelet count >150 000/mm³ because of a low prevalence of varices at risk of bleeding.
- This meta-analysis found that patients with low liver stiffness and normal platelet count have a four- to fivefold lower risk of varices and of varices at risk of bleeding than those with high liver stiffness or low platelet count.
- Varices at risk of bleeding are found in no more than 4% when liver stiffness is low and platelet count normal.

2 | MATERIALS AND METHODS

2.1 | Literature search

Medline (PubMed), Embase, Cochrane library and manual searches were combined and last performed on September 26, 2016. Key searching terms were "Baveno", "oesophageal varices", "varices", "portal hypertension", "liver stiffness", "transient elastography", "FibroScan" and "platelet". Terms were combined within each database. General reviews and references from published trials were also used. The exact search term combinations can be found in the Appendix S1. Duplicate were excluded. No language restriction was applied. Two observers (A.M. and P.D.) also screened all abstracts presented between 2013 and 2016 at the Liver Meeting of the American Association for the Study of Liver Diseases (AASLD) and the International Liver Congress of the European Association for the Study of the Liver (EASL).

2.2 | Criteria for inclusion and exclusion of studies

Prospective and retrospective observational studies were included. To reduce risks of bias, strict inclusion and exclusion criteria were defined prior to the literature search. To be considered, a study had to: (a) include patients with cirrhosis or compensated advanced liver disease; (b) provide data relative to the presence of varices according to a given cut-off for liver stiffness and platelet count. When several publications were found covering the same study population, only the most recent was taken into account.

2.3 | Endpoints and criteria for combinability

Endpoints were defined prior to the beginning of the meta-analysis. Main endpoints were the presence of varices and the presence of varices at risk of bleeding. In this study, varices were considered at risk of bleeding when they were described as "large", "grade 2 or grade 3", "high-risk gastro-esophageal varices (diameter >5 mm and/or presence high-risk stigmata)", "small with red signs", "medium-large varices", "varices needing treatment" or "gastric varices felt to warrant prophylactic treatment".

2.4 | Data extraction

Data extraction was performed independently by two investigators (A.M. and P.D.) using standardized data collection forms. Discrepancies in data interpretation were resolved by discussion, re-review of the studies and consultation with one other author when necessary.

2.5 | Quality score

The methodological quality of studies was assessed using the Newcastle Ottawa Scale for cohort studies.[12]

2.6 | Statistical analysis

We used a random effects model to obtain a summary estimate of primary outcomes among patients with low liver stiffness and normal platelet count and among those with either high liver stiffness or low platelet count. The random model was chosen because it takes into account the possibility of heterogeneity between studies.[13] Data on all patients were extracted to allow intention-to-treat analyses. Difference between groups was expressed by odds ratios (ORs) and their 95% confidence interval (95% CI). A P <.05 was considered

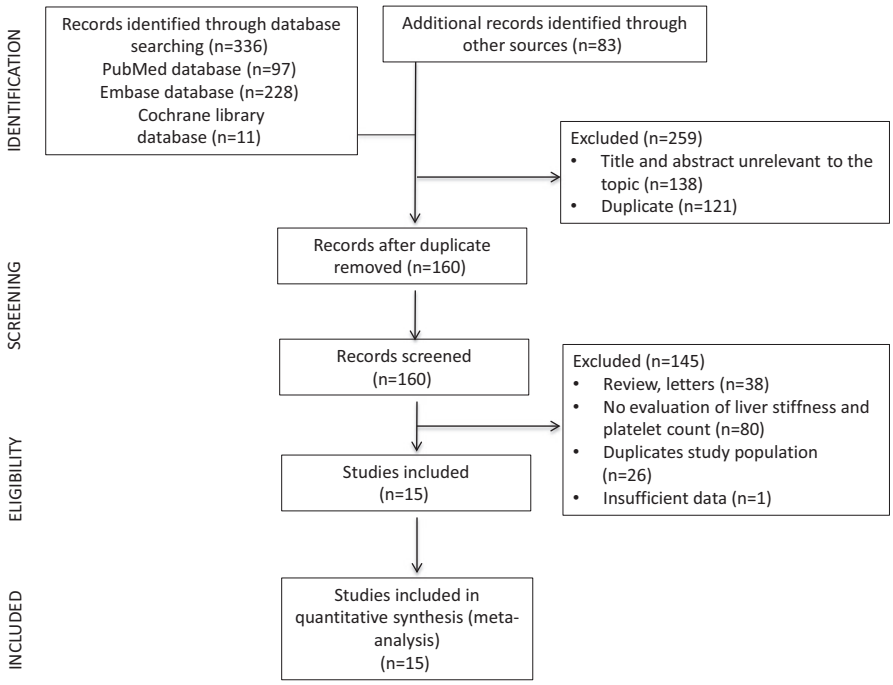


FIGURE 1 Flow chart of the selection of studies for inclusion in the meta-analysis

statistically significant. We also calculated event rates among patients with low liver stiffness and normal platelet count, a measure of how often a particular statistical event occurs within a group of an experiment, and their 95% CI, as already done elsewhere.[14,15]

In a first step, an overall meta-analysis was performed. In a second step, a subgroup meta-analysis including only published studies was performed. In a third step, a subgroup meta-analysis including only prospective studies was performed.

Heterogeneity was assessed by Cochran's *Q* test[16] and the I^2. More specifically, the I^2 statistic was used to estimate inconsistency in meta-analyses, representing the percentage of the between-study variability due to heterogeneity rather than chance.[17] A significant Cochran's *Q*-statistic (below 0.10) was chosen as a threshold for significant heterogeneity across studies. The following cut-offs were used to quantify heterogeneity with the I^2statistic: 0-25%, low; 25-50%, moderate; >50%, high heterogeneity.[17] In cases of moderate or high heterogeneity, the methodological section of each study was re-reviewed to determine whether any discrepancy could be identified, and sensitivity analyses excluding the discrepant study were performed. To assess the extent of publication bias, the Egger test and the Begg and Mazumdar test were used.[16,18] A P <.05 was considered statistically significant. All statistical analyses were performed using Comprehensive Meta-analysis (Biostat, Englewood, NJ).

3 | RESULTS

3.1 | Study population

Figure 1 summarizes the flow chart of the selection of studies for inclusion in the meta-analysis. We screened 419 references; 160 were selected for full-text retrieval. Of these, 15 were included in the analysis.[2,7-11,19-27]

Table 1 summarizes the main characteristics of the studies included in the meta-analysis. There were 997 patients with low liver stiffness and normal platelet count and 2367 patients with either high liver stiffness or low platelet count.

3.2 | Study quality

Table S1 details the quality of the studies included.

3.3 | Methodological assessment of studies

Six studies had been published and nine were available only in abstract form. Five were prospective and 10 retrospective (Table 1). The definition of varices at risk of bleeding differed between studies (Table 2).

The methodological analysis of each study identified discrepancies in nine studies (Table 1).

All studies excepting five used a liver stiffness cut-off of 20 kPa and a platelet cut-off of 150 000/mm^3 for estimating the risk of varices, as recommended in the 2015 Baveno guidelines[6] (Table 2). Two studies used a cut-off of 25 kPa for liver stiffness.[2,19] One study used a cut-off of 120 000/mm^3 for platelet count.[23] Two studies used a cut-off of 25 kPa for liver stiffness and a cut-off of 100 000/mm^3 for platelet count.[7,24] In case of moderate or high heterogeneity, sensitivity analyses excluding the Abraldes[19] the Augustin,[2] the Ding,[7] the Montes Ramirez[23] and the Puigvehi[24] studies were performed.

All studies excepting five included mainly patients with cirrhosis due to chronic viral infection (Table 1). In one study, the aetiology of the liver disease was not specified.[9] In three studies, cirrhosis was mainly related to liver diseases other than chronic viral infections.[11,20,21] In case of moderate or high heterogeneity, sensitivity analyses excluding the Perazzo,[9] the Ahmed,[20] the Cales[21] and the Paternostro[11] studies were performed.

TABLE 1 Characteristics of the 15 studies included

References	Study design	N	Alcoholic cirrhosis (%)	Viral-related cirrhosis (%)	NAFLD-related cirrhosis (%)	Male (%)	Age (y)	Child–Pugh class A (%)	Delay between liver stiffness measurement and upper gastrointestinal endoscopy
Abraldes (2016)[19]	Retrospective study	379	14[f]	70[f]	6[f]	NA	58[a]	100	NA
Ahmed (2016)[20]	Retrospective study	478	36	33[g]	21	NA	54[a]	NA	≤1 y
Augustin (2014)[2]	Prospective study	49	NA	89[g]	NA	44[h]	62[a,h]	NA	≤1 mo
Cales (2016)[21]	Prospective study	31	64[f]	26[f]	4[f]	72[f]	55[a,f]	NA	NA
Chang (2016)[22]	Retrospective study	173	NA	55	NA	62	56[a]	100	≤1 y
Ding (2015)[7]	Retrospective study	271	12	69	8	70	57-59[c]	100	3.4 mo[b]
Gomez (2016)[10]	Retrospective study	160	NA	93	NA	65	57[a]	100	NA
Maurice (2016)[8]	Retrospective study	310	13	62	14	67	58[b]	89	≤1 y
Montes Ramirez (2012)[23,i]	Retrospective study	85	0	100	0	76	45[b]	78	≤6 mo
Paternostro (2016)[11]	Retrospective study	92	30	47	NA	73	53[a]	100	NA
Perazzo (2015)[9]	Prospective study	97	NA	NA	NA	NA	59[a]	80	≤1 d
Puigvehi (2016)[24]	Prospective study	368	0	100	0	63	57-58[d]	100	NA
Silva (2016)[25]	Retrospective study	112	7	83	NA	77	54[b]	87	≤1 y
Thabut (2016)[26]	Prospective study	649	0	100	0	73	55-56[e]	100	NA
Tosetti (2016)[27]	Retrospective study	146	0	100	0	NA	NA	100	NA

NA, not available; NAFLD, non-alcoholic liver disease.

[a]Expressed as mean.

[b]Expressed as median.

[c]In this study, age was expressed as median. Two cohorts were studied. In the training cohort (n=71), median age was 59 y. In the validation cohort (n=200), median age was 57 y.

[d]In this study, age was expressed as median. In the group of patients with high-risk varices (n=55), median age was 57 y. In the group of patients without high-risk varices (n=313), median age was 58 y.

[e]In this study, age was expressed as median. In the group of patients with progression of portal hypertension (n=150), median age was 56 y. In the group of patients without progression of portal hypertension (n=498), median age was 55 y.

[f]These data refer to the whole study population.

[g]Patients with viral-related cirrhosis had cirrhosis related to chronic hepatitis C virus infection.

[h]These data refer to the whole study population of 54 patients with a liver stiffness ≥13.6 kPa.

[i]This study included 63 HIV-positive individuals.

TABLE 2 Presence of any varices and varices at risk of bleeding among the 15 studies included

References	Cut-off for liver stiffness (kPa)	Cut-off for platelet count (/mm³)	Definition of varices at risk of bleeding	Groups of patients	N	N with varices	N with varices at risk of bleeding
Abraldes (2016)[19,a]	25	150 000	Small varices with red signs, large varices	Patients with low liver stiffness and normal platelet count	87	12	3
				Patients with either high liver stiffness or low platelet count	292	147	54
Ahmed (2016)[20]	20	150 000	Large varices, grade 2 varices, small varices with red wales, gastric varices to warrant beta blocker prophylaxis	Patients with low liver stiffness and normal platelet count	111	NA	3
				Patients with either high liver stiffness or low platelet count	367	NA	49
Augustin (2014)[2,a]	25	150 000	Grade 2 or 3 oesophageal varices, varices with red signs	Patients with low liver stiffness and normal platelet count	10	0	0
				Patients with either high liver stiffness or low platelet count	39	5	0
Cales (2016)[21,b]	20	150 000	Large varices	Patients with low liver stiffness and normal platelet count	31	4	0
				Patients with either high liver stiffness or low platelet count	NA	NA	NA
Chang (2016)[22]	20	150 000	Large varices	Patients with low liver stiffness and normal platelet count	34	NA	3
				Patients with either high liver stiffness or low platelet count	139	NA	11
Ding (2015)[7]	25	100 000	Varices diameter > 5 mm and/or with the presence of high-risk stigmata	Patients with low liver stiffness and normal platelet count	107	26	0
				Patients with either high liver stiffness or low platelet count	164	64	26
Gomez (2016)[10,c]	20	150 000	NA	Patients with low liver stiffness and normal platelet count	115	8	NA
				Patients with either high liver stiffness or low platelet count	45	17	NA
Maurice (2016)[8]	20	150 000	Oesophageal varices≥grade 2, gastric varices	Patients with low liver stiffness and normal platelet count	102	11	2
				Patients with either high liver stiffness or low platelet count	208	61	13
Montes Ramirez (2012)[23,d]	20	120 000	Grade 2 or 3 varices	Patients with low liver stiffness and normal platelet count	13	0	0
				Patients with either high liver stiffness or low platelet count	72	38	NA

(Continues)

TABLE 2 (Continued)

References	Cut-off for liver stiffness (kPa)	Cut-off for platelet count (/mm³)	Definition of varices at risk of bleeding	Groups of patients	N	N with varices	N with varices at risk of bleeding
Paternostro (2016)[11,e]	20	150 000	Large varices	Patients with low liver stiffness and normal platelet count	10	4	0
				Patients with either high liver stiffness or low platelet count	80	56	19
Perazzo (2015)[9]	20	150 000	Large varices, varices with red signs	Patients with low liver stiffness and normal platelet count	21	6	0
				Patients with either high liver stiffness or low platelet count	76	48	NA
Puigvehi (2016)[24]	25	100 000	Varices diameter > 5 mm and/or with the presence of high-risk stigmata	Patients with low liver stiffness and normal platelet count	149	NA	10
				Patients with either high liver stiffness or low platelet count	219	NA	45
Silva (2016)[25]	20	150 000	Varices requiring treatment, small varices with red signs, large varices	Patients with low liver stiffness and normal platelet count	12	2	0
				Patients with either high liver stiffness or low platelet count	100	52	20
Thabut (2016)[26,f]	20	150 000	Grade 2 or 3 oesophageal varices	Patients with low liver stiffness and normal platelet count	156	15	0
				Patients with either high liver stiffness or low platelet count	493	182	49
Tosetti (2016)[27]	20	150 000	Varices requiring prophylactic treatment	Patients with low liver stiffness and normal platelet count	39	9	0
				Patients with either high liver stiffness or low platelet count	107	57	12

NA, not available.
[a]Data extracted from table 5.2 of ref.[28].
[b]Data extracted from Panel A of the poster presented during the 2016 International Liver Congress. Available data did not enable us to extract the number of patients with high liver stiffness or low platelet count with or without varices, as well as the number of patients with high liver stiffness or low platelet count with or without varices at risk of bleeding.
[c]Data extracted from table 2 of the poster presented during the 2016 International Liver Congress.
[d]This study considered the presence of oesophageal varices or portal hypertensive gastropathy.
[e]Data extracted from figure 2 of the poster presented during the 2016 International Liver Congress. This study included 82 patients but two patients had no information on varices size.
[f]Data extracted from the communication presented during the 2016 International Liver Congress.

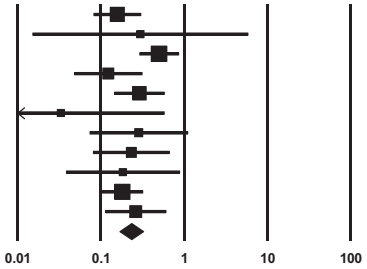
3.4 | Outcomes

3.4.1 | Risk of presenting varices

Patients with low liver stiffness and normal platelet count had a lower risk of varices than did patients with either high liver stiffness or low platelet count (OR=0.23, 95% CI=0.17-0.32, P<.001, Figure 2A and Table 2). This corresponds to a 4.3-fold risk reduction for varices in patients with low liver stiffness and normal platelet count compared to patients with either high liver stiffness or low platelet count. There was a moderate heterogeneity between studies (P=.2, I^2=28%). The sensitivity, specificity, negative predictive value and positive predictive value of

(A)

Study name	Subgroup within study	Statistics for each study					With varices/total	
		Odds ratio	Lower limit	Upper limit	Z-value	P-value	With low liver stifness and normal platelet count	With high liver stifness or low platelet count
Abraldes 2016	All varices	0.158	0.082	0.303	−5.558	.000	12/87	147/292
Augustin 2014	All varices	0.299	0.015	5.859	−0.796	.426	0/10	5/39
Ding 2016	All varices	0.502	0.292	0.862	−2.496	.013	26/107	64/164
Gomez 2016	All varices	0.123	0.048	0.315	−4.378	.000	8/115	17/45
Maurice 2016	All varices	0.291	0.146	0.583	−3.487	.000	11/102	61/208
Montes Ramirez 2012	All varices	0.033	0.002	0.579	−2.334	.020	0/13	38/72
Paternostro 2016	All varices	0.286	0.074	1.105	−1.815	.069	4/10	56/80
Perazzo 2015	All varices	0.233	0.081	0.670	−2.703	.007	6/21	48/76
Silva 2016	All varices	0.185	0.038	0.886	−2.112	.035	2/12	52/100
Thabut 2016	All varices	0.182	0.104	0.319	−5.937	.000	15/156	182/493
Tosetti 2016	All varices	0.263	0.114	0.607	−3.129	.002	9/39	57/107
Pool estimate risk		0.234	0.169	0.323	−8.840	.000		



(B)

Study name	Subgroup within study	Statistics for each study			Total
		Event rate	Lower limit	Upper limit	
Abraldes 2016	All varices	0.138	0.080	0.227	12/87
Augustin 2014	All varices	0.045	0.003	0.448	0/10
Cales 2016	All varices	0.129	0.049	0.297	4/31
Ding 2016	All varices	0.243	0.171	0.333	26/107
Gomez 2016	All varices	0.070	0.035	0.133	8/115
Maurice 2016	All varices	0.108	0.061	0.184	11/102
Montes Ramirez 2012	All varices	0.036	0.002	0.384	0/13
Paternostro 2016	All varices	0.400	0.158	0.703	4/10
Perazzo 2015	All varices	0.286	0.134	0.508	6/21
Silva 2016	All varices	0.167	0.042	0.477	2/12
Thabut 2016	All varices	0.096	0.059	0.153	15/156
Tosetti 2016	All varices	0.231	0.125	0.387	9/39
Pool estimate rate		0.152	0.108	0.211	

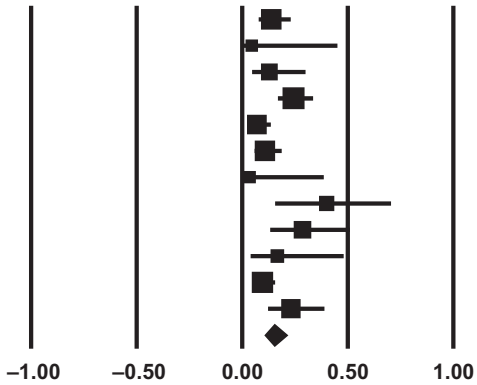


FIGURE 2 Risk of varices. (A) Pooled estimate risk of varices between patients with low liver stiffness and normal platelet count and those with either high liver stiffness or low platelet count. (B) Pooled estimate rate for varices in patients with low liver stiffness and normal platelet count. CI, confidence interval; OR, odd ratio

high liver stiffness or low platelet count to identify varices were 0.887, 0.379, 0.862 and 0.434 respectively. The results of sensitivity analyses excluding studies that did not use a liver stiffness cut-off of 20 kPa or a platelet count cut-off of 150 000/mm^3 and the results of sensitivity analyses excluding studies that did not mainly include patients with viral-related cirrhosis are provided in Table S2. In the sensitivity analysis including only studies using a cut-off for liver stiffness of 20 kPa and a cut-off for platelet count of 150 000/mm^3, patients with low liver stiffness and normal platelet count had a lower risk of varices than did patients with either high liver stiffness or low platelet count (OR=0.21, 95% CI=0.15-0.29, *P*<.001, corresponding to a 4.8-fold risk reduction for varices) with no heterogeneity between studies (*P*=.8, I^2=0%). No publication bias was detected by the Egger test (*P*=.3) or by the Begg and Mazumdar test (*P*=.5). In the subgroup analysis including only published studies, patients with low liver stiffness and normal platelet count had a lower risk of varices than did patients with either high liver stiffness or low platelet count (OR=0.26, 95% CI=0.15-0.45, *P*<.001, corresponding to a 3.8-fold risk reduction for varices) with moderate heterogeneity between studies (*P*=.09, I^2=48%). Results of subgroup analyses including only prospective studies are reported in Table S3.

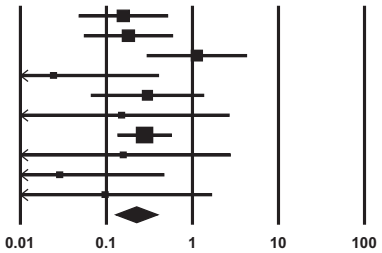
The pooled estimate rate for varices was 0.15 (95% CI=0.11-0.21, Figure 2B and Table 2) for patients with low liver stiffness and normal platelet count. There was a high heterogeneity between studies (*P*=.003, I^2=62%). The results of sensitivity analyses excluding studies that did not use a liver stiffness cut-off of 20 kPa or a platelets cut-off of 150 000/mm^3 and the results of sensitivity analyses excluding studies that did not mainly include patients with cirrhosis related to viral infection are provided as Table S2. These analyses did not eliminate heterogeneity between studies. In the subgroup analysis including only published studies, the pooled estimate rate for varices was 0.16 (95% CI=0.10-0.25) for patients with low liver stiffness and normal platelet count, with high heterogeneity between studies (*P*=.04, I^2=57%). Results of subgroup analyses including only prospective studies are reported in Table S3.

3.4.2 | Risk of varices at risk of bleeding

Patients with low liver stiffness and normal platelet count had a lower risk of varices at risk of bleeding than did patients with either high liver stiffness or low platelet count (OR=0.22, 95% CI=0.13-0.39, *P*<.001,

(A)

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-value	P-value	With varices/total: With low liver stifness and normal platelet count	With varices/total: With high liver stifness or low platelet count
Abraldes 2016	High risk varices	0.157	0.048	0.517	–3.048	.002	3/87	54/292
Ahmed 2016	High risk varices	0.180	0.055	0.590	–2.831	.005	3/111	49/367
Chang 2016	High risk varices	1.126	0.296	4.281	0.174	.862	3/34	11/139
Ding 2016	High risk varices	0.024	0.001	0.403	–2.593	.010	0/107	26/164
Maurice 2016	High risk varices	0.300	0.066	1.355	–1.565	.118	2/102	13/208
Paternostro 2016	High risk varices	0.150	0.008	2.682	–1.289	.197	0/10	19/80
Puigvehi 2016	High risk varices	0.278	0.135	0.572	–3.480	.001	10/149	45/219
Silva 2016	High risk varices	0.157	0.009	2.765	–1.265	.206	0/12	20/100
Thabut 2016	High risk varices	0.029	0.002	0.468	–2.493	.013	0/156	49/493
Tosetti 2016	High risk varices	0.097	0.006	1.673	–1.606	.108	0/39	12/107
Pool estimate risk		0.224	0.128	0.391	–5.241	.000		



(B)

Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Total
Abraldes 2016	High risk varices	0.034	0.011	0.102	3/87
Ahmed 2016	High risk varices	0.027	0.009	0.080	3/111
Augustin 2014	High risk varices	0.045	0.003	0.448	0/10
Cales 2016	High risk varices	0.016	0.001	0.206	0/31
Chang 2016	High risk varices	0.088	0.029	0.240	3/34
Ding 2016	High risk varices	0.005	0.000	0.070	0/107
Maurice 2016	High risk varices	0.020	0.005	0.075	2/102
Montes Ramirez 2012	High risk varices	0.036	0.002	0.384	0/13
Paternostro 2016	High risk varices	0.045	0.003	0.448	0/10
Perazzo 2015	High risk varices	0.023	0.001	0.277	0/21
Puigvehi 2016	High risk varices	0.067	0.036	0.120	10/149
Silva 2016	High risk varices	0.038	0.002	0.403	0/12
Thabut 2016	High risk varices	0.003	0.000	0.049	0/156
Tosetti 2016	High risk varices	0.013	0.001	0.171	0/39
Pool estimate rate		0.040	0.027	0.059	

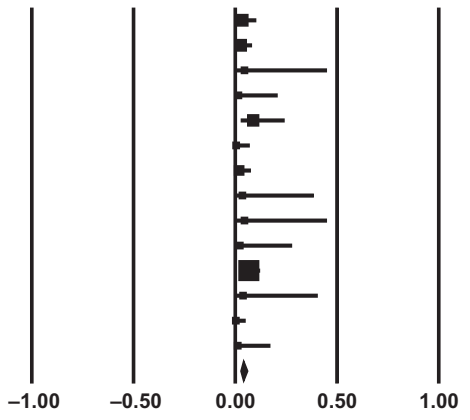


FIGURE 3 Risk of varices at risk of bleeding. (A) Pooled estimate risk of varices at risk of bleeding between patients with low liver stiffness and normal platelet count and those with either high liver stiffness or low platelet count. (B) Pooled estimate rate for varices at risk of bleeding in patients with low liver stiffness and normal platelet count. CI, confidence interval; OR, odd ratio

Figure 3A and Table 2). This corresponds to a 4.5-fold risk reduction for varices at risk of bleeding in patients with low liver stiffness and normal platelet count compared to patients with either high liver stiffness or low platelet count. There was a low heterogeneity between studies (P=.25, I^2=21%). The sensitivity, specificity, negative predictive value and positive predictive value of high liver stiffness or low platelet count to identify varices at risk of bleeding were 0.934, 0.296, 0.974 and 0.137 respectively. No publication bias was detected by the Egger test (P=.15) or by the Begg and Mazumdar test (P=.5). In the subgroup analysis including only published studies, patients with low liver stiffness and normal platelet count had a lower risk of varices at risk of bleeding than did patients with either high liver stiffness or low platelet count (OR=0.16, 95% CI=0.06-0.43, P<.001, corresponding to a 6.2-fold risk reduction for varices at risk of bleeding) with low heterogeneity between studies (P=.3, I^2=16%). Results of subgroup analyses including only prospective studies are reported in Table S3.

The pooled estimate rate for varices at risk of bleeding was 0.040 (95% CI=0.027-0.059, Figure 3B and Table 2) for patients with low liver stiffness and normal platelet count. There was a low heterogeneity between studies (P=.4, I^2=3%). When excluding studies that did not use a liver stiffness cut-off of 20 kPa or a platelet cut-off of 150 000/mm^3, the pooled estimate rate for varices at risk of bleeding was 0.031 (95% CI=0.017-0.055) with no heterogeneity between studies (P=.5, I^2=0%). In the subgroup analysis including only published studies, the pooled estimate rate for varices at risk of bleeding was 0.025 (95% CI=0.012-0.052) for patients with low liver stiffness and normal platelet count, with no heterogeneity between studies (P=.8, I^2=0%). Results of subgroup analyses including only prospective studies are reported in Table S3.

4 | DISCUSSION

The recent availability of non-invasive tools to diagnose cirrhosis is increasing the number of patients presenting with compensated cirrhosis. A significant number of unnecessary endoscopies will be performed in patients with a low risk of varices if current practice habits are not modified.[28] In April 2015, the Baveno VI conference recommended avoiding upper gastrointestinal endoscopy in patients with compensated cirrhosis when liver stiffness is <20 kPa

and platelets count >150 000/mm³.[6,28] Since then, several studies have been conducted to validate these recommendations. A meta-analysis was therefore required to synthesize available data. This meta-analysis found that patients with low liver stiffness and normal platelet count had a 4 to 5-fold lower risk of presenting varices and varices at risk of bleeding than patients with either high liver stiffness or low platelet count. Of note, even if the definition of varices at risk of bleeding was not the same in all studies, the average estimate rate of varices at risk of bleeding was 4% in patients with low liver stiffness and normal platelet count, and 3% for those patients included in studies that did use the same cut-offs for liver stiffness and platelet count as those recommended in the Baveno VI guidelines. As a result, these criteria adequately identify patients with a very low risk of bleeding. In line with these findings, a recent study found that an increase in liver stiffness >20 kPa or a decrease in platelet count <150 000/mm³ was associated with the apparition of new varices or with the progression of small varices already documented.[26] Thus, liver stiffness and platelet count should be assessed at regular intervals to reevaluate if an upper gastrointestinal endoscopy would be indicated.

Several lines of evidence indicate that the underlying liver disease might have influenced the performance of the combined use of low liver stiffness and normal platelet count for ruling out varices. First, the cut-off values of liver stiffness for predicting cirrhosis vary according to the underlying cause of liver disease.[29] Second, the aetiology of cirrhosis has a strong impact on the liver stiffness cut-off for the diagnosis of large varices.[30] Third, clinical characteristics and outcomes of patients with cirrhosis differ according to the underlying liver disease.[31] A high incidence of complications related to portal hypertension has been reported in patients with cirrhosis related to alcoholic liver disease.[32,33] Hence, whether the Baveno VI criteria have similar predictive value depending on the aetiology of the liver disease remains to be established. As most of available data concerned patients with chronic hepatitis B or C viral infection, further studies are needed to validate the Baveno VI criteria in patients with alcoholic liver disease or non-alcoholic steato-hepatitis. Individual participant data regarding the aetiology of the underlying liver disease would be of interest; however, this information was not available. In addition, it should be kept in mind that most of the studies have been performed in populations of patients with compensated liver disease in which the probability of varices at risk of bleeding was limited. Hence, the conclusions of the present meta-analysis only apply to patients with compensated liver disease.

A limitation of this study is related to the fact that among the 15 studies included, nine were available only in abstract form. However, pooling together abstracts and full papers has already been made.[34] It may reduce the publication bias consisting in the probability of less frequently reporting negative studies as full paper. In addition, the pooling approach enabled analysis of the most recent studies that have been terminated but not yet published. Finally, the results did not differ whether we consider the meta-analysis of all 15 studies or the subgroup analysis of the six published studies. Another classical limitation of meta-analyses is related to the presence of heterogeneity that may prevent making robust conclusions and recommendations. It suggests that a substantial proportion of the difference in the effect between studies cannot be explained only because of random sampling but because of true differences between studies. In this meta-analysis, low heterogeneity was found for the analysis on the risk of varices at risk of bleeding according to liver stiffness and platelet count and for the analysis of the estimated rate of varices at risk of bleeding in patients with low liver stiffness and normal platelet count. Of note, no significant heterogeneity was identified between studies in the analyses related to the risk of varices at risk of bleeding although the definition of such varices differed between studies. There was no heterogeneity in sensitivity analysis on the risk of varices when only the studies using the same criteria as those recommended in the Baveno VI guidelines were included. However, heterogeneity was observed in sensitivity analyses related to the rate for varices among patients with low liver stiffness and normal platelet count, suggesting that factors other than those taken into account in these analyses may have influenced the outcomes.

In summary, the combined use of liver stiffness and platelet count allows for the identification of patients with compensated advanced liver disease that have a low risk of bleeding. Less than 4% of these patients have varices at risk of bleeding when liver stiffness is <20 kPa and platelet count >150 000/mm³. Additional longitudinal prospective studies are required to identify potential risk factors leading to the development of varices at risk of bleeding in these patients.

CONFLICTS OF INTEREST

The authors do not have any disclosures to report.

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