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A comprehensive systematic review and meta-analysis of risk factors for rebleeding following device-assisted enteroscopy therapy of small-bowel vascular lesions

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ABSTRACT

Introduction: the aim of this study was to determine the risk factors for rebleeding following device-assisted enteroscopy therapy of small bowel vascular lesions.

Methods: this is a systematic review and meta-analysis. A literature search was performed from January 2003 to October 2019. All studies reporting on at least one

risk factor for bleeding recurrence after endoscopic therapy of small bowel vascular lesions were included. A meta-analysis of those risk factors reported in at least three studies was performed to assess their association with rebleeding. The OR and 95 % CI were used for binary outcome data. Heterogeneity analysis was performed using the Tau and I^2 index. If I^2 > 20 %, potential sources of heterogeneity were identified by sensitivity analyses and a random-effect model was used.

Results: the search identified a total of 572 articles and 35 full-text records were assessed for eligibility after screening. Finally, eight studies that included 548 patients were selected. The overall median rebleeding rate was 38.5 % (range: 10.9-53.3 %) with a median follow-up of 24.5 months. Female sex (OR: 1.96, 95 % CI: 1.14-3.37, p = 0.01, I^2 = 0 %), Osler-Weber syndrome (OR: 4.35, 95 % CI: 1.22-15.45, p = 0.02, I^2 = 0 %) and cardiac disease (OR: 1.89, 95 % CI: 1.12-2.97, p = 0.005, I^2: 0 %) were associated with rebleeding. According to the sensitivity analysis, overt bleeding (OR: 2.13, 95 % CI: 1.22-3.70, p = 0.007, I^2 = 0 %), multiple lesions (OR: 4.57, 95 % CI: 2.04-10.22, p < 0.001, I^2 = 0 %) and liver cirrhosis (OR: 2.61, 95 % CI: 1.11-6.13, p = 0.03, I^2 = 0 %) were also predictors for rebleeding.

Conclusions: patient characteristics and comorbidities should be considered for follow-up patient management after effective device-assisted endoscopic therapy, as they can predict rebleeding.

Keywords: Small bowel bleeding. Angioectasia. Obscure gastrointestinal bleeding. Device-assisted enteroscopy.

INTRODUCTION

Small bowel vascular lesions (SBVLs) are the leading cause of SB bleeding (SBB) (1) and angioectasias are the most common finding in this scenario. They can be multiple, with different bleeding potentials and are usually located in the proximal SB (2).

Long-term outcomes after positive and negative capsule endoscopy (CE) have been reported (3-5). In addition, the risk factors for recurrence in patients with SB bleeding (SBB) who underwent CE have been addressed by several studies. Niikura et al. (6) reported that female gender, liver cirrhosis, warfarin use, overt bleeding and positive

CE findings were significant predictors of rebleeding. Vascular lesions have also been described as an independent risk factor for recurrence (7). However, most of these studies do not consider the impact of an endoscopic treatment during follow-up. In addition, the different types of SB lesions (vascular, ulcerative, polyps, tumors, etc.) may have different bleeding profiles and recurrence rates.

Device-assisted enteroscopy (DAE) is widely recognized as the first-line therapeutic procedure in SBVLs (8). However, achieving an effective treatment can be challenging. A systematic review of 18 studies published in 2015 found rebleeding rates of 43.8 % (range: 24-67 %) (9), concluding that endoscopic therapy may not impact on bleeding recurrence. Similarly, the rebleeding rate did not differ by positive CE results or the application of interventional treatments in a multicenter study of 305 patients (10). Conversely, other studies reported the benefit of DAE in decreasing SBB recurrence, even after a second endoscopic treatment (11,12). Thus, there are probably other factors that influence the rebleeding rate and could potentially determine the outcome of these patients.

The aim of the present systematic review and meta-analysis was to determine the risk factors for rebleeding following DAE therapy of SBVLs.

METHODS

Search strategy

A literature search was performed in Medline (through PubMed), Scopus and the Cochrane Library from January 1st 2003 to October 14th 2019. The medical terms "vascular lesion OR vascular lesions OR angioectasia OR angioectasias OR angiodysplasia OR angiodysplasias OR Dieulafoy OR telangiectasia OR telangiectasias AND enteroscopy OR double-balloon OR DBE OR single-balloon OR SBE" were used.

Two authors (EPCR, GP) independently selected the studies and assessed them for eligibility. Any disagreements were resolved by reviewing the article and were settled by consensus with a third author (GR). A citing reference search of the included studies and a manual search in Google Scholar were also performed. All human studies with adult populations (> 18 years old) and published in English, Spanish, Portuguese or French were considered. Duplicate studies were removed.

The full text reading of selected studies was performed according to the inclusion and exclusion criteria following the initial screening by title and abstract. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was considered. The present review and meta-analysis research protocol was prospectively registered in the PROSPERO database (ID: 149384).

Inclusion and exclusion criteria

All studies reporting on at least one risk factor for bleeding recurrence after DAE therapy for SBVL in adult patients (≥ 18 years-old) were considered according to the PICO framework, regardless of the endoscopy therapy performed. Conversely, those studies that considered the risk factors for rebleeding of SB lesions without providing data on SBVL were excluded. The studies that reported on patients with SBVL treated by conventional upper-GI endoscopes were also excluded. Meeting abstracts, reviews, editorials, opinions, letters and surveys were excluded. Studies that reported less than ten cases were not considered.

Data extraction and Quality Assessment

Data extraction was performed using a standardized collection sheet by two authors (EPCR, GP). The study characteristics collected included year of publication, study period, primary country of the study, study design, number of patients, mean age and sex distribution. The rebleeding rate of patients who underwent endoscopic therapy as well as those lost to follow-up were noted. Rebleeding was defined either as the need for red blood cell transfusion, the presence of overt digestive bleeding (melena, hematemesis, hematochezia) or a decrease in the hemoglobin concentration of more than 1-2 g/dl, after exclusion of all other causes of anemia. All risk factors for rebleeding in the univariate analysis were collected as dichotomous data. The corresponding author was contacted when the study only provided data of hazard ratio or odds ratio (OR) indices.

Risk of bias (quality) assessment was independently assessed (LEZN, GB) with the Newcastle-Ottawa quality Assessment scale (NOS). The quality scores of studies ranged from zero to nine in three categories (selection, comparability, and outcome).

The study quality was classified according to the study score as poor (0-3), moderate (4-6) and high (7-9). No study was excluded based on this score, although a sensitivity analysis to account for the effect of poor-quality studies was planned.

Statistical analysis

Statistical analyses were performed with the RevMan v.5.3 (Cochrane Library, Oxford, UK) and SPSS v.24 (IBM, SPSS, IL, USA) programs. When means and/or standard deviations were not reported in the original paper, they were estimated from reported medians, ranges and sample size as described by Hozo (13). A meta-analysis for those risk factors reported in at least three studies was performed. The OR and 95 % CIs were used for binary outcome data. Heterogeneity analysis was performed using the Tau and I^2 index. If I^2 > 20 %, potential sources of heterogeneity were identified by sensitivity analyses that were performed by omitting one study at a time and investigating the influence on the overall pooled estimate. The random effect model was applied in those studies with I^2 > 20 %, due to the suspicion of heterogeneity among different risk factors in outcome definitions. Potential publication biases were assessed by funnel-plot visual analysis. A two-sided p-value < 0.05 was considered as statistically significant.

RESULTS

Study characteristics

The literature search identified a total of 572 articles and 35 full-text records were assessed for eligibility after screening. Finally, eight studies (14-21) with 548 patients from Europe (n = 4, 50 %) and Asia (n = 4, 50 %) were included in the present meta-analysis, as shown in the flow-chart (Fig. 1). All of them were observational studies and only one had a prospective design (17). The prospective study had one-year of follow-up and also the highest number of patients (n = 183). Jeon et al. (14) only considered angioectasias and not all SBVLS. Study characteristics are shown in table 1.

The overall median rebleeding rate was 38.5 % (range: 10.9-53.3 %). Overall, the median of the mean follow-up time was 24.5 months (12-58), considering all but one study where the follow-up was unknown (21). Endoscopic therapy was performed by

argon plasma coagulation and/or clipping in all cases (14-21) by DBE (14-21) or SBE (15). In most of cases, an anterograde approach was performed. The Spirus enteroscopy was also used in one patient (15). Other techniques such as sclerosing injections or bipolar coagulation (15,19) were also used.

Risk factors assessment

Most of the original articles assessed many potential risk factors. However, there were two reports in which only one risk factor was considered and extracted (16,20). The definitions of demographic variables, bleeding presentation (overt/occult), Osler-Weber syndrome and lesion type according to Yano-Yamamoto (22) classification were homogeneous among different studies. The number of SBVLs was extracted as solitary or multiple (18,21) and the authors were contacted when this information was not provided in the manuscript. The threshold was different within different studies such as ≥ ten angioectasias (14), mean (17), median (15) or total number of SBVLs (19).

Data on chronic renal disease were extracted in five studies (14,15,17-19) and was defined as patients on hemodialysis in only one study (18). Liver cirrhosis (14,17-19) and chronic liver disease (15) terms were pooled as the same variable. Cirrhosis or portal hypertension were considered together by Samaha et al. (19). Cardiac disease included ischemic heart, valvular and arrhythmic diseases (14,15,17). Samaha et al. (19) considered ischemic and valvular/arrhythmic diseases as independent risk factors but both were pooled as cardiac disease in the current meta-analysis to ensure homogeneity with other studies.

Anti-aggregation and anticoagulation therapies were extracted and analyzed in three studies (15,17,19). Anti-aggregation and anticoagulation were collected as the only risk factor in some studies (14,18,19). All patients under anticoagulation therapy were treated with warfarin in the study of Shinozaki et al. (11). Rahmi et al. (17) considered anticoagulation or antiplatelet therapy taken during the entire follow-up and also present at the end of the study.

Transfusion requirements were not included in the quantitative synthesis due to the high heterogeneity in the definition within the studies evaluating this variable (14,15,17,19-21). In fact, transfusion was considered as the overall number of blood

units with a limit of ≥ 1 (15,19,20), ≥ 3 (14) or ≥ 4 (17), or the amount of blood unit transfused as a quantitative variable (15,21). Similarly, NSAIDs intake (15,19), diabetes (14,15,19) and hypertension (14,15,19) were not considered for the meta-analysis as they were reported in less than three studies or data extraction was not possible.

Risk factors for rebleeding

All included studies reported a higher rebleeding rate in female patients and pooled female sex (OR: 1.96, 95 % CI: 1.14-3.37, p = 0.01, I^2 = 0 %) was also associated with rebleeding (Fig. 2). Overt bleeding presentation was associated with rebleeding in a single study (17), but this association was not observed in the pooled analysis. The Osler-Weber syndrome (OR: 4.35, 95 % CI: 1.22-15.45, p = 0.02, I^2 = 0 %) was also more frequent in patients with bleeding recurrence as shown in figure 3 and this difference was statistically significant. However, the lesion type or the presence of multiple lesions were not associated with rebleeding after endoscopic therapy.

Cardiac disease was pooled in four studies including 359 patients (Fig. 4) and was also a risk factor for rebleeding using both a fixed-effect and random-effect models (OR: 1.89, 95 % CI: 1.12-2.97, p = 0.005, I^2 = 0 %). Chronic renal disease and liver cirrhosis were not associated with this outcome. No single study showed an association between anti-aggregation or anticoagulation and rebleeding during follow-up and pooled data confirmed these results (Fig. 5).

Sensitivity analysis

With regard to the bleeding presentation, overt bleeding was associated with rebleeding (OR: 2.13, 95 % CI: 1.22-3.70, p = 0.007, I^2 = 0 %) if the study from Samaha et al. (19) was omitted (14,15,17). Three single studies reported a statistically significant association between the presence of multiple SBVLs and rebleeding (18,19,21) and only one (15) did not report this result. Considering only these three authors, the presence of multiple lesions was a risk factor for rebleeding (OR: 4.57, 95 % CI: 2.04-10.22, p < 0.001, I^2 = 0 %). Liver cirrhosis was also associated with rebleeding when the study from Shinozaki et al. (2014) (18) was not included in the pooled analysis (OR: 2.61, 95 % CI: 1.11-6.13, p = 0.03, I^2 = 0 %). All these results (Supp. Fig. 1)

were consistent using random- and fixed-effect models.

Quality assessment and publication bias

The assessment of study quality based on NOS (23) resulted in high (n = 3) and moderate (n = 5) scores. Funnel-plots were assessed for all pooled risk factors and they were symmetrical with no evidence of publication bias (Supp. Fig. 2).

DISCUSSION

The present systematic review and meta-analysis of eight observational studies from Asia and Europe showed that female sex, Osler-Weber syndrome and cardiac disease are risk factors associated with rebleeding, following the endoscopic therapy of SBVLs by DAE. In addition, overt-bleeding presentation, the presence of multiple SBVLs and liver cirrhosis were associated with this outcome according to the sensitivity analysis.

In the clinical practice, the most relevant parameter to assess the effectiveness of endoscopic therapy in SBVLs seems to be the rebleeding rate. However, the evaluation of real rebleeding that originates from the SB is challenging and the theoretical concept could be far from the daily practice. Similar concerns have been drawn after medical therapy or surgery in this setting (24). In fact, the concept of rebleeding does not consider if the bleeding source or location are the same as in the baseline episode. Consequently, a same patient may undergo a “successful therapy” and a new episode of SB bleeding originating from a new lesion. In addition, rebleeding is probably underdiagnosed, as these episodes can be missed because they do not meet the criteria; i.e., they do not require blood transfusions or they do not have significant anemia. Furthermore, the recurrence should not be considered as clinical failure in all cases. In many patients with a high comorbidity burden (25) and recurrent bleeding, the aim of endoscopic therapy would be to prevent clinically relevant bleedings endangering the patient’s life, increase the interval between blood transfusions, IV iron supplementation and redo enteroscopy.

In the present meta-analysis, the overall rebleeding rate was between 10.9 and 53.3 % in the included studies. This wide range was probably due to the heterogeneity in the definition, the population characteristics and the different complete enteroscopy and

follow-up rates. The endoscopic therapy was fairly homogeneous in all studies. However, the description of the bleeding potential of the treated SBVL was lacking in most of reports and may have also influenced the results.

In our study, the median of the mean follow-up was 24.5 months (12-58), considering all but one study (21). The median delay at first rebleeding ranged from 32.5 months to 36 months, but it was only described in two studies (14,19). A suitable analysis of this data was therefore not possible. In our analysis, we focused on factors associated with rebleeding but a complementary analysis of factors associated with early rebleeding would be of great interest. To date, such valuable data is lacking. In the clinical practice, it would allow a better screening of patients at high risk of early rebleeding, leading to a more aggressive follow-up strategy.

Overall, most studies that analyzed the risk factors for rebleeding included in our study were retrospective. Older age is a known factor associated with the presence of SBVLs (26). However, the different threshold used in the included studies prevented a pooling of this demographic variable. Patients with cardiac disease were at risk of rebleeding in our meta-analysis. These patients may be under anti-aggregation or anticoagulation therapies (17), overestimating this association. In addition, patients with valvular and ischemic diseases may have different risk profiles for rebleeding. However, in our study, anticoagulation or anti-aggregation were not associated with rebleeding and the association between cardiac disease and rebleeding was consistent after sensitivity analysis. In addition, we pooled valvular and ischemic diseases together following the definition of the included reports. In the daily practice, stopping anticoagulation or double anti-aggregation is often considered after the first SBB. However, in the present meta-analysis, anticoagulation therapy may have been stopped in higher-risk patients with a severe first SBB episode (without ongoing anticoagulation), and continued in those with non-severe SBB. Thus, leading to a selection bias. There was no information in the studies about how many patients had an indication for anticoagulation, although there was no ongoing treatment after the first episode due to the high estimated risk of rebleeding. The types and doses of anticoagulation therapy and the combination of anticoagulation and anti-aggregation could also have influenced these results. Thus, although there was no statistically

significant association with rebleeding in our meta-analysis, these results should be taken with caution.

Overt bleeding presentation and multiple lesions were also associated with rebleeding in the sensitivity analysis. The presence of multiple lesions has also been described as an independent predictor for rebleeding by Sakai E et al. (27). Furthermore, the number of SBVL viewed by DAE and on previous CE (17) can be an important feature and not only if they were single or multiple. Finally, emergency enteroscopy was not analyzed as a potential risk factor for rebleeding in the included articles. However, the endoscopic therapy of SBVL in this particular setting is challenging and could probably have an increased risk of recurrence, as the rebleeding rate has been described to be high, the underlying lesions usually have a high potential for bleeding (e.g., Dieulafoy's lesion) and some of them can be missed due to the massive bleed (28,29).

Our review has several limitations. An individual participant data meta-analysis could have been a better approach to identify confounders. Moreover, although we have included eight studies in the quantitative synthesis, each individual risk factor was considered in only 3-5 reports and the definitions were lacking or incomplete in some cases. However, this is the first systematic review in this setting and we performed a sensitivity analysis with consistent results.

In conclusion, patient characteristics and comorbidities should be considered in patients who undergo endoscopic therapy for SBVL. Female sex, Osler-Weber syndrome, overt-bleeding presentation, the presence of multiple SBVLs and liver cirrhosis can increase the risk of rebleeding. A dedicated follow-up by early CE or a more aggressive therapeutic approach could be an option in these cases.

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Table 1. Study characteristics of the eight included publications for quantitative synthesis

Patients presenting with at least one small bowel vascular lesion who underwent endoscopic therapy by device-assisted enteroscopy with endoscopy follow-up. CRD:

Study, year	*Design*	*Country*	*Patients*	*Rebleeding rate*	*Follow-up*	*Risk factors included in the meta-analysis*	*NOS score*
Ran Jeon, 2017 (14)	Retrospective, multicenter	Korea	45	15.6 %	(Mean, SD) 94.1 ± 131.3 weeks	Sex, bleeding presentation, CRD, LC	7
Pinho R, 2016 (15)	Retrospective, single-center	Portugal	35	40 %	(Median, interquartile range) 23 months (9-43)	Sex, bleeding presentation, Osler-Weber syndrome, type of lesion, solitary/multiple, CRD, LC, CD, antiaggregation, anticoagulation	6
Igawa A, 2015 (16)	Retrospective, single-center	Japan	64	10.9 %	(Mean, SD) 54 ± 30 1a lesions 53 ± 25 1b lesions	Type of lesion	5
Rahmi G, 2014 (17)	Prospective, multicenter	France	183	35 %	1 year	Bleeding presentation, CRD, LC, CD, antiaggregation, anticoagulation	7
Shinozaki S, 2014 (18)	Retrospective, single center	Japan	43	37 %	(Mean, SD, range) 4.9 (1.7) years, (2.4-9.1)	Sex, type of lesion, solitary/multiple, CRD, LC, CD	7
Samaha E, 2012 (19)	Retrospective, single center	France	98	46 %	(Median, SD, range)	Sex, bleeding presentation, Osler-	6

chronic renal disease; LC: liver cirrhosis; CD: cardiac disease; NOS: Newcastle-Ottawa quality assessment scale.

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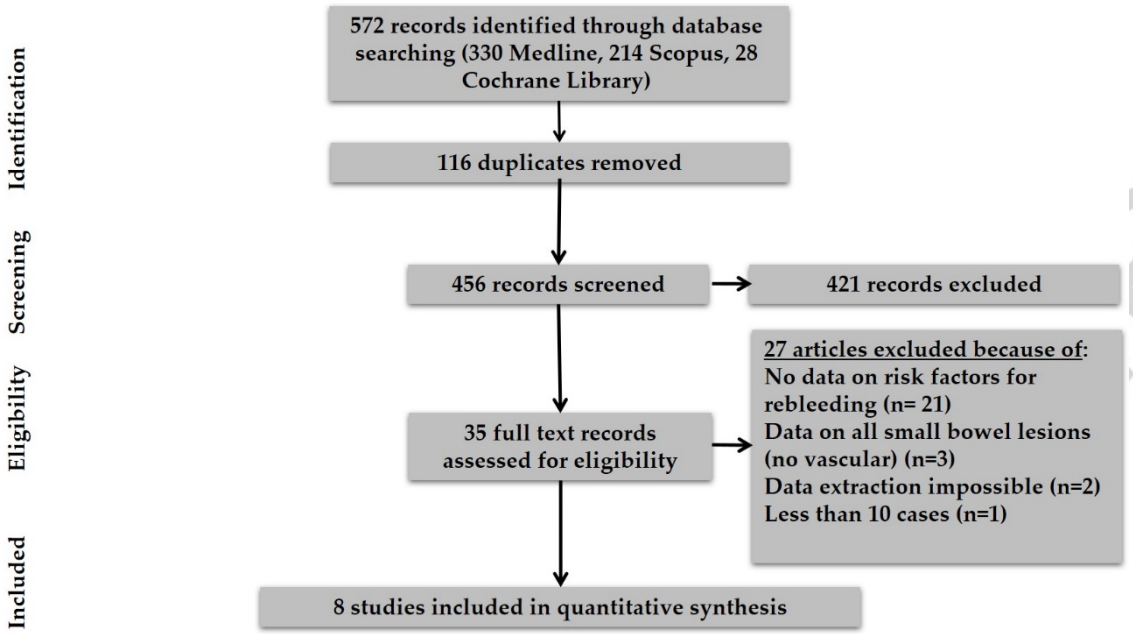

Fig. 1. Flow-chart of the search strategy and inclusion of the studies according to the PRISMA statement.

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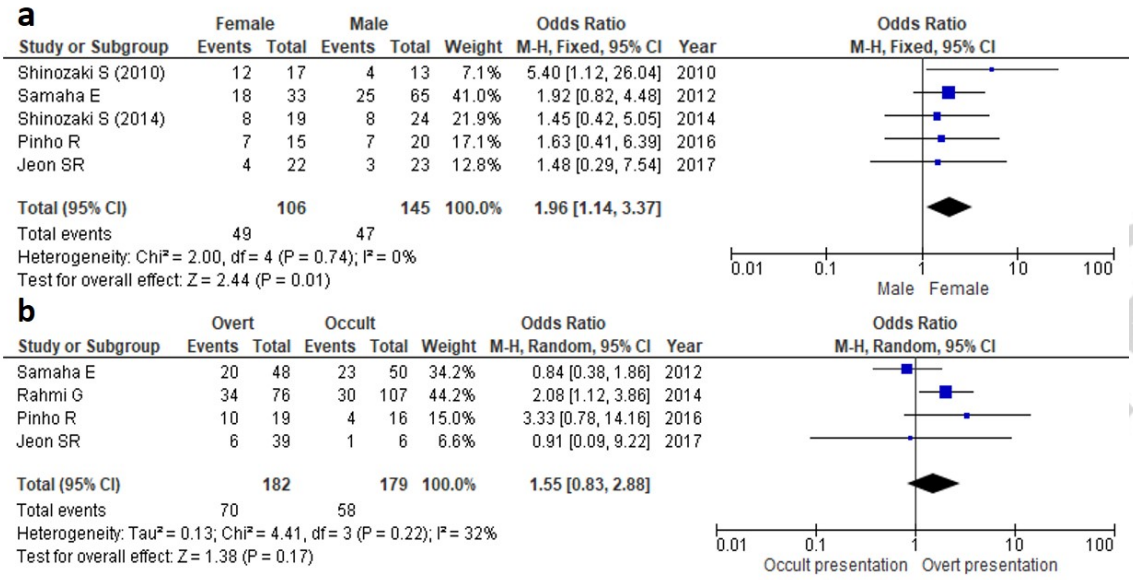

Fig. 2. Pooled rebleeding rates following device-assisted enteroscopy therapy of small bowel vascular lesions according to sex (A) and bleeding presentation (B).

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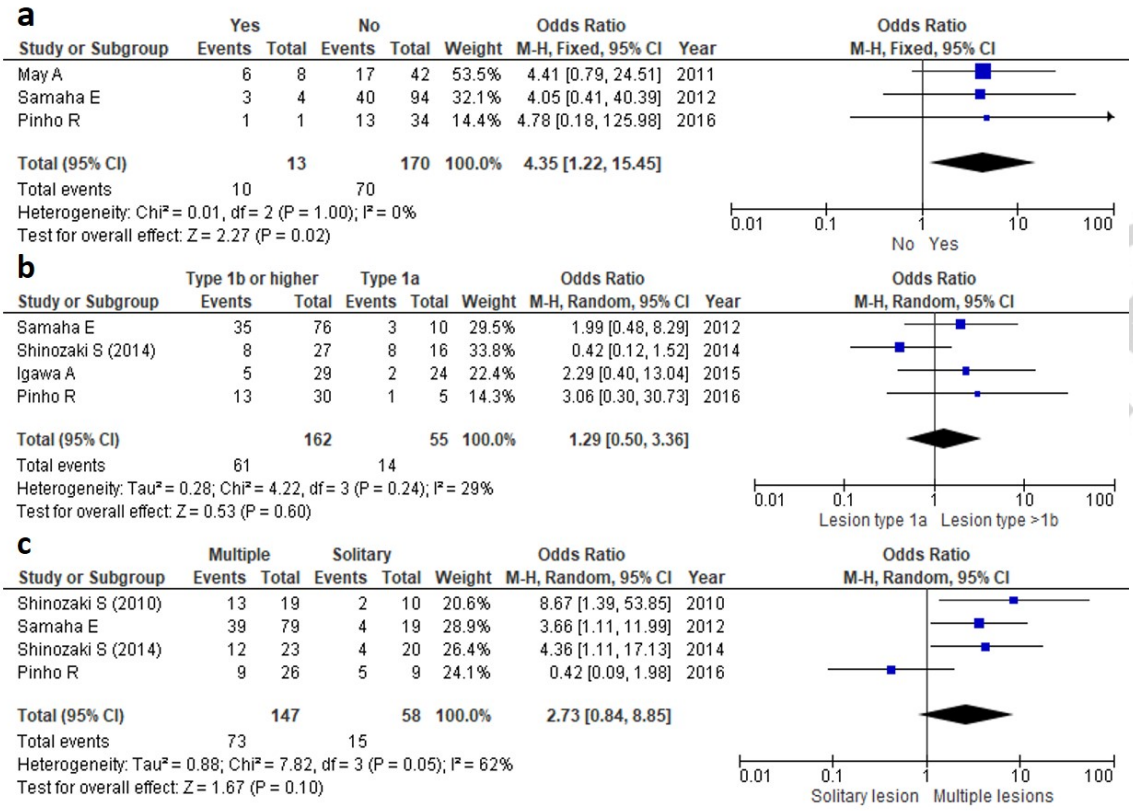

Fig. 3. Forest plot of the risk factors of rebleeding following device-assisted enteroscopy therapy of small bowel vascular lesions according to the presence of Osler-Weber syndrome (A) lesion type according to Yano-Yamamoto classification (B) and solitary or multiple lesions (C).

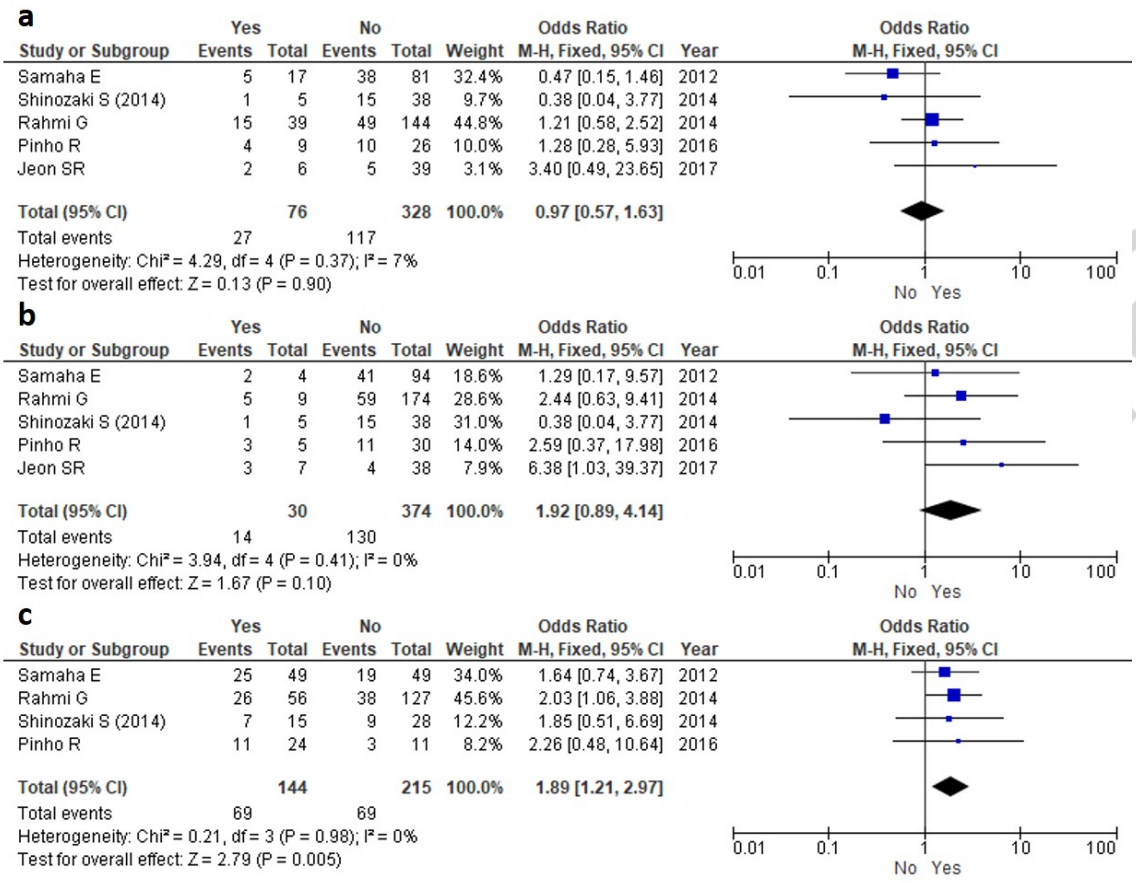

Fig. 4. Forest plot of the risk factors of rebleeding following device-assisted enteroscopy therapy of small bowel vascular lesions according to the presence of chronic renal disease (A), liver cirrhosis (B) and cardiac disease (C).

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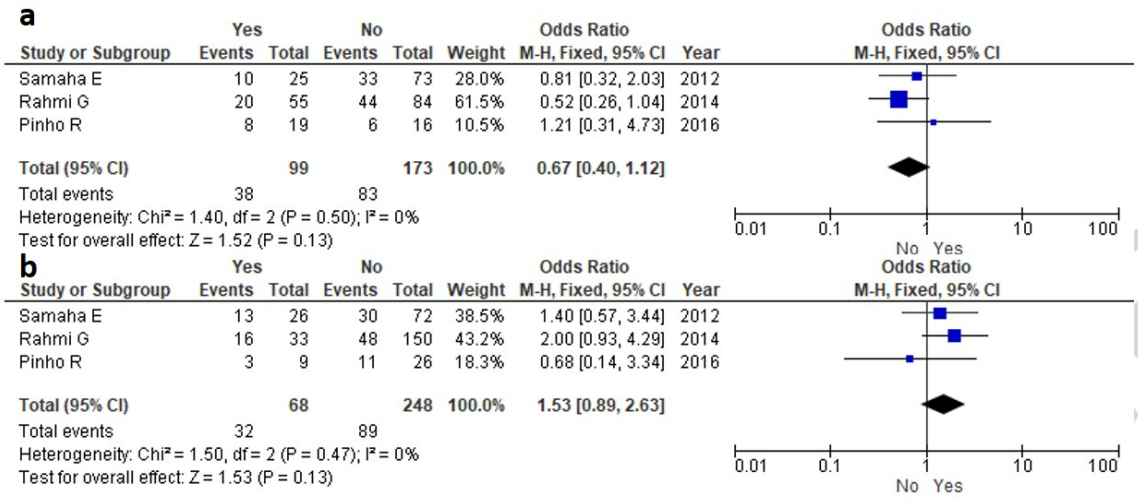

Fig. 5. Pooled rebleeding rates (events/total) in patients under anti-aggregation (A) or anticoagulation therapy (B) who underwent endoscopic therapy of small bowel vascular lesions.

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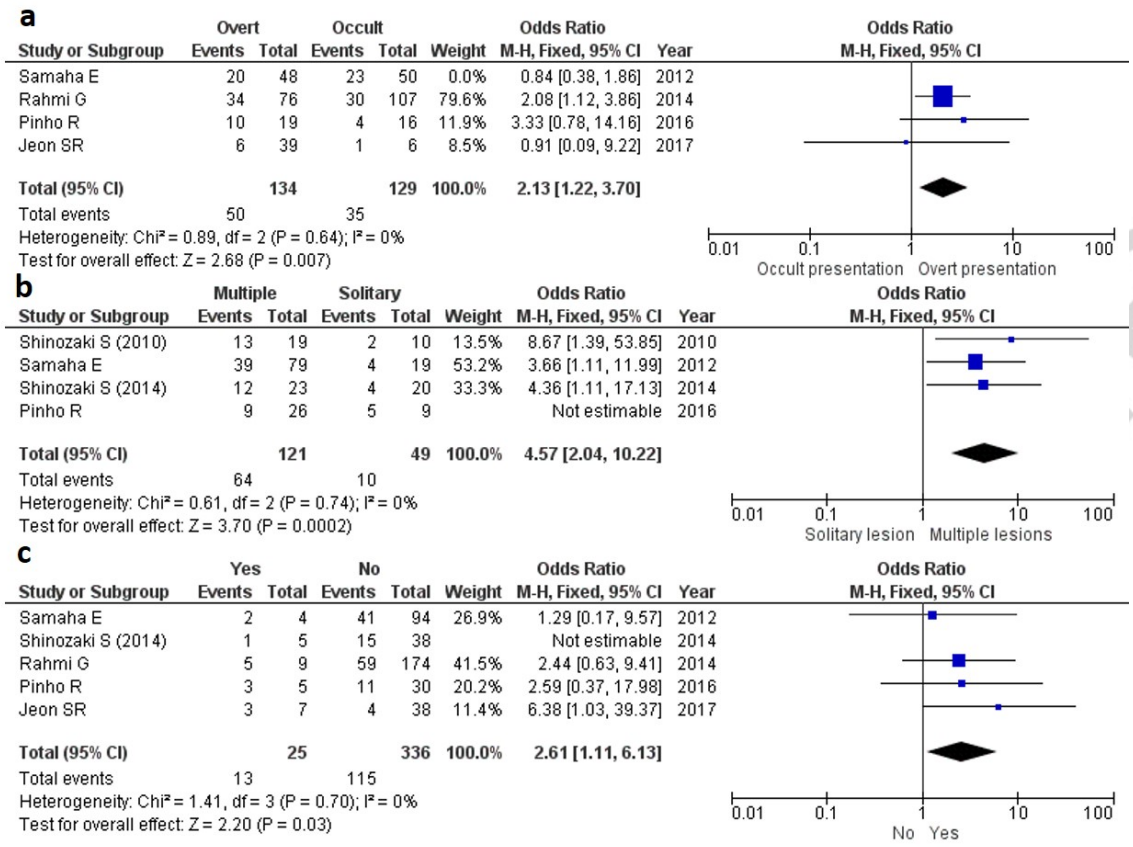

Supp. Fig. 1. Sensitivity pooled analysis by excluding one study due to overt bleeding presentation (A), multiple lesions (B) and liver cirrhosis (C).

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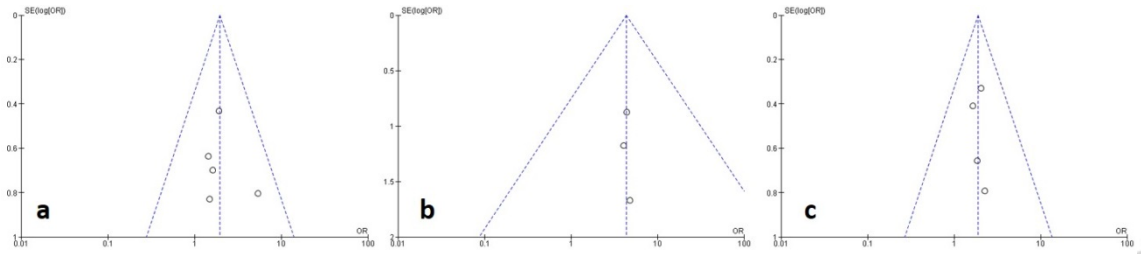

Supp. Fig. 2. Publication bias analysis by funnel plots in the most relevant factors associated with rebleeding such as female sex (A), Osler-Weber syndrome (B) and cardiac disease (C). No significant publication bias was found.